

ANNALS OF INTERNAL MEDICINE

CARL VERNON WELLER

Editor

VOLUME 5

(OLD SERIES, VOLUME X)

ANN ARBOR, MICHIGAN

1932

Contents

NUMBER 1, JULY, 1931

The Clinical Significance of So-Called Chronic Appendicitis JULIUS FRIEDENWALD and THOMAS H MORRISON	1
Early Diagnosis of Neoplasms of the Digestive Tract THOMAS R BROWN	9
Studies on the Mechanism of the Pain of Peptic Ulcer FRID M SMITH and W D PAUL	14
Rheumatoid Arthritis RUSSELL L CICH	23
A Diagnostic Triad in Syphilitic Aortitis C S DANZER	29
Agranulocytosis Its Classification, with Cases and Comments STEWART R ROBERTS and ROY R KRACKI	40
An Evaluation of the Skin Test in Allergy H L ALEXANDER	52
The Influence of the Practitioner of Medicine in Guiding the Public Towards Health HAVEN EMMERSON	57
The General Practitioner and the Public Health Program FELIX J UNDERWOOD	65
Editorials	70
Abstracts	74
Reviews	77
College News Notes	80

NUMBER 2, AUGUST, 1931

Chronic Myocardial Insufficiency and Its Therapeutic Management HENRY A CHRISTIAN	95
Circulatory Adjustments in Heart Disease SOMA WEISS	100
Dissecting Aneurysms of the Aorta PAUL C SAMSON	117
The Treatment of Pernicious Anemia with Desiccated Stomach and with Liver Extract CYRUS C STURGIS and RAPHAEL ISAACS	131
The Adequate Treatment of Anemia GEORGE R MINOT and WILLIAM B CASTLE	159
Complement Fixation in the Diagnosis of Amebiasis CHARLES F GRAIG	170
Pathological Classification of Goiter W CARPENTER MACCARTY	178
The Heart in Hyperthyroidism HENRY M THOMAS, JR	184
Medical Aspects of Peptic Ulcer ALBERT F R ANDRESEN	192
Malignant Melanoma with Delayed Metastatic Growths D L WILBUR and H R HARTMAN	201
The Hospital Its Relation to the Community and to the Medical Pro- fession WINFORD H SMITH	212
The Profession and the Public GEORGE EDWARD FOLLANSBEE	224
Editorials	231
Abstracts	234
Reviews	236
College News Notes	238

NUMBER 3, SEPTEMBER, 1931

Observations on Rheumatic Pancarditis and Infective Endocarditis W S THAYER	247
A Theory of the Causation of Cardiac Pain ALEXANDER LAMBERT	256
The Insulin Coefficient, an Improved Method for the Clinical Control of Diabetes Mellitus JOHN R WILLIAMS	264
The Effect of the Ingestion of Burdock on Normal and Diabetic Individu- als—A Preliminary Report A A SILVER and JOHN C KRANTZ	274
Diabetes in the Negro Race EUGENE J LEOPOLD	285
Syphilitic Aortitis in Retrospect WILLIAM S MIDDLETON	294
Bronchiomoniasis A Clinical and Pathological Study with Report of Illustrative Cases OTIS S WARR	307
Post-Vaccination Encephalitis CHARLES ARMSTRONG	333
Clinical Aspects of Portal Cirrhosis ALBERT M SNELL	338
Hereditary Ectodermal Dysplasia of the Anhidrotic Type WILLIAM H GORDON and ROBERT C JAMIESON	358
The Application of a Modified Psychiatric Approach in the Treatment of Certain Gastrointestinal Disorders THEODORE H MORRISON and SAMUEL MORRISON	371
The Prestige of the Internist MILES J BREUER	381
Editorial	385
Abstracts	389
Reviews	391
College News Notes	393

NUMBER 4, OCTOBER, 1931

Variations in Manifestations of Rheumatic Fever in Relation to Climate WARFIELD T LONGCOPE	401
Colonic Changes in Chronic Arthritis W H DICKSON	408
Total Occlusion of the Right Branch of the Pulmonary Artery by an Or- ganized Thrombus J H MANS and T B MALLORY	417
The Therapeutic Use of Oxygen in Heart Disease ALVAN L BARACH	428
The Reaction to Nitrites in the Anginal Syndrome and Arterial Hyper- tension ALIX M BURGESS	441
Ventricular Flutter and Complete Heart Block with Restoration of Sinus Rhythm and A-V Conduction LESLIE T GAGER	463
Primary Aplastic Anemia, a Discussion and Report of Two Cases JAMES B CARLY and JOSEPH H TAYLOR	471
The Use of Sulphur for the Production of Fever in Peripheral Vascular Disease LORENZ M WALLER and EDGAR V ALLEN	478
Mediastinal Displacement in Pneumothorax W C POLLOCK	486
Treatment of Recurrent Erysipelas HAROLD L AMOSS	500
The Historical Development of the Present Conception of Cardiac Condi- tions in Exophthalmic Goiter A MORRIS GINSBERG	505
Books	518
Notes	524
College News Notes	526
	530

NUMBER 5, NOVEMBER, 1931

The Vital Hormone of the Adrenal Cortex FRANK A. HARTMAN, BYRON D. BOWEN, GEO. W. THORN and CLAYTON W. GRIGG	539
The Relation of the Parathyroid Glands to Calcium Metabolism HOWARD A. BRIGER and DAVID P. BARR	552
The Etiology and Treatment of Diabetes Insipidus T. B. FUTCHER	566
The Level of Oxygen Exchange in Obesity as a Factor in Planning Treatment FRANK A. EVANS	574
The Many Sided Question of Protein in Nephritis W. S. McCANN	579
Mountain Fever and Spotted Fever of the Rocky Mountains—Clinical Studies NOXON TOOMLA	585
American Mountain Tick-Fever and Spotted Fever of the Rocky Mountains—Comparative Epidemiography NOXON TOOMLA	601
Thrombo-Angitis Obliterans Among Persons Past Middle Age BAYARD T. HORTON and GEORGE E. BROWN	613
Treatment of Angina Pectoris With a Tissue Vasodilator Extract Preliminary Report JOSEPH B. WOLFE, DONALD FINDLAY and EDWARD DISSIN	625
Medulloblastoma Cerebelli KARL ROTHSCHILD	643
Electrocardiographic Studies of the Effects of Propylene as a General Anesthetic in Man MORRIS H. KAHN and LLOYD K. RIGGS	651
Editorials	659
Abstracts	663
Reviews	665
College News Notes	668

NUMBER 6, DECEMBER, 1931

Observations on Pneumococcus Type III Pneumonia FRANCIS G. BLAKE	673
Tularemia Pneumonia H. H. PERMAR and W. W. G. MACLACHLAN	687
Experimentally Produced Lesions of the Liver JESSE L. BOLLMAN and FRANK C. MANN	699
Further Studies in Allergic Migraine, Based on a Series of Two Hundred and Two Consecutive Cases RAY M. BALLET and HERBERT J. RINKIL	713
Diet as a Factor in the Etiology of Anemia RICHARD A. KERN	729
Anemia Associated with Gastrointestinal Disorders Clinical Considerations and the Value of Iron in Treatment CHESTER S. KEEFER	740
On the Morbid Anatomy of the Diaphragm BALDWIN LUCKÉ	750
The Heart and the Diaphragm I. M. TRACE	759
Malignancy in the Lung, Including Seven Primary Carcinomas in the Lung with Autopsy Findings HENRY MONROE MOSES	765
The Dietetic Treatment of Tuberculosis ERNEST S. MARIETTE	793
Editorials	803
Abstracts	807
Reviews	809
College News Notes	813

NUMBER 7, JANUARY, 1932

Quinidine Therapy in the Treatment of Cardiac Irregularities Due to Hyperthyroidism	J P ANDERSON	825		
Tachycardia	CHAS W BARRIER	829		
The Response of the Cardiovascular System to Respiratory Strain	A Measure of Myocardial Efficiency	ALLAN EUSTIS	842	
Auricular Paroxysmal Tachycardia Caused by Digitalis	Report of a Case	ARTHUR F HRYL	858	
Medical and Surgical Problems Associated with Coronary Sclerosis	ARLIE R BARNES	873		
Pulmonary Infections by the Friedlander's Bacillus (Bacillus Mucosus Capsulatus)	FRANK FREMMEL, KARL J HENRICHSEN and HENRY C SWIANY	886		
Syphilis of the Lung	Report of a Case with Autopsy Findings	HAROLD COMFORT DENMAN	895	
Observations on the Contour of Normal and Tuberculous Female Chests	S A WEISMAN	907		
American Mountain Tick-Fever	Semeiography and Nosology	With Remarks on Pathology and Treatment	NOXON TOOMEY	912
Bilateral Double Kidney with Duplication of Ureters	ROBERT M LINTZ	924		
Editorial		932		
San Francisco—The City by the Golden Gate		935		
Abstracts		943		
Reviews		945		
College News Notes		948		

NUMBER 8, FEBRUARY, 1932

Multiple Arterial Occlusions	HAROLD W DANA	955
Hereditary Deforming Chondrodysplasia. Case Report	M A SPANGEL-PIRGER	962
The Dietetic Control of Some Points of Hypertension and the Associated Gastrointestinal and Nervous Symptoms	V C ROWLAND	971
An Evaluation of Stool Vaccines in Chronic Irritable Colon Therapy	JOHN G MATHER and JAMES I BALTZ	982
Diagnostic Value of Secretory Function in Gastric Disease Various Methods Studied and Compared	ERNEST H GAITHER	992
The Clinical Significance of Choroidal Tubercles	R T PATON	997
Laboratory Methods in Clinical Medicine Report of Three Cases (1) Diaphragmatic Eventration, (2) Chronic Nephritis without Hypertension Cardiac Hypertrophy, or Retinal Changes, (3) Unusual Case of Cholelithiasis	SAMUEL LRVINE	1000
Atrioventricular Nodal Rhythm. With Report of Cases	CARL V VISCHEP and LOWELL L LANE	1010
Some Disorders of Functional Origin	S KATZENELBOGEN	1017
Advanced Pulmonary Tuberculosis	LEWIS J MOORMAN	1022
The Diagnosis of Hyperthyroidism	MAYNARD E HOLMES	1028
Hero Worship and the Propagation of Fallacies	C S BUTLER	1033
Editorial		1039
College News Notes		1041
Report on the San Francisco Meeting		1043
		1045
		1048

NUMBER 9, MARCH, 1932

Cutaneous Manifestations of Systemic Diseases	UDO J WILE	1103
Malignant Thymoma of Reticulum-Cell Type with Pressure on the Left Lung, Trachea, Esophagus, Left Phrenic and Left Recurrent Laryngeal Nerves, and with Metastases to the Glands of the Left Side of the Neck, Importance of Biopsy for Differential Diagnosis of Cervical Lymphadenopathies	LAWRENCE F BARKER	1113
The Management of Severe and of Atypical Hyperthyroidism	FRANK H LAMM	1123
Fallacies and Dangers in the Treatment of Exophthalmic Goiter by Iodine	WILLARD OWEN THOMPSON and PHILIP K THOMPSON	1129
Subacute Bacterial Endocarditis Following the Extraction of Teeth Report of a Case	MITCHELL BERNSTEIN	1138
The Management of Coronary Thrombosis and its Complications	BLANTON P SIWARD	1145
Paroxysmal Tachycardia Related to the Menstrual Period	J HAMILTON CRAWFORD LOUIS H SUGER, and H FRUCHTER	1155
The Coincidental Occurrence of Diabetes Mellitus and Pernicious Anemia Report of Two Cases	CHARLES SHOOKOFF	1161
The Significance of Meningeal Permeability	S KATZMACHBGEN	1168
The Use of Histamin HCl as a Test Meal	HENRY H HART	1175
San Francisco as a Medical Center	Wm J KERR	1178
Editorial		1196
Abstracts		1198
Reviews		1200
College News Notes		1203

NUMBER 10, APRIL, 1932

The Relation of the Intestinal Tract and Diet to the Treatment of Arthritis	RALPH PIMBERTON and E G PRICE	1221
Toxic Granulocytopenia Purpura Hemorrhagica and Aplastic Anemia Following the Arsphenamines	ADOLPH B LOVEMAN	1238
Ascending Paralysis Resulting from the Drinking of "Jamaica Ginger" A Clinical Study of Fifty Cases	DILLBERT H WILDEN	1257
Peripheral Vascular Diseases Treatment with Acetyl-Choline Hydrochloride	W C WATERS	1267
Metastatic Malignant Tumors of the Brain	HAROLD F DUNLAP	1274
Ephedrine in the Treatment of Narcolepsy	HARRY A COLLINS	1289
Typhus-Like (Spotted) Fever from Tick-Bite, Rocky Mountain Spotted Fever Type, Identified with a Symbiont <i>Proteus</i> -Like Septicemia	NOXON TOOMEY	1296
Post-Pneumonic Lung Abscess Resembling Lung Tumor, with Case Report	GEORGE F COOPER	1308
Modern Conception of Retinal Detachment with its Relation to Internal Medicine	C A CLAPP	1313
How to Obtain More Autopsies	D SCHUYLER PULFORD	1315
Editorial		1321
Abstracts		1324
Reviews		1326
College News Notes		1329

The Clinical Significance of So-Called Chronic Appendicitis*†

By JULIUS FRIEDENWALD, M.D., F.A.C.P., and THEODORE H. MORRISON, M.D., F.A.C.P., Baltimore, Maryland

ANY conflicting views concerning the significance of chronic appendicitis have been held during the past 10 to 15 years. While some clinicians have attributed many disturbances occurring in the abdomen to this cause, others have held that it in itself has but slight clinical significance. According to the latter conception, so-called chronic appendicitis is not a disease in which the symptoms are due entirely to the appendix alone, but one in which many other abdominal as well as other factors play an important rôle.

It is a well recognized fact, that since the advent of roentgenology numerous variations in the size, shape and position of the appendix have been observed, which have been recorded as chronic changes in this organ. In a considerable number of these reports, great significance has been attached to these findings as a probable cause of many digestive symptoms. Operation has been frequently undertaken upon the basis of

*From the Gastro-Enterological Clinic of the Department of Medicine, University of Maryland.
†Delivered at the Baltimore Meeting of the American College of Physicians, March 23, 1931

If the embryology of the appendix is carefully studied, the cause of many errors in diagnosis becomes apparent. This organ is derived from the cecum as a pouch about the seventh or eighth week of fetal life. The cecum occupies a high position under the liver during early development but descends lower later and drags the appendix down with it. The appendix finally assumes its position in the right iliac fossa, but the attachment to the cecum may vary markedly. In 90 per cent of instances, according to Treves, it occupies a mediodorsal position. The direction of the appendix is determined by the position of the attachment as well as the length of the mesoappendix. It may be directed posterior or lateral to the cecum and colon or into the pelvis beneath the terminal ileum or upward in the direction of the gall bladder. The meso-

NUMBER 11, MAY, 1932

1337	Rheumatic Heart Disease A Review CLOUGH TURKILL BURNETT	1337
1357	Early Manifestations of Rheumatic Infections in Young Children C C McLEAN	1357
1367	Causes, Classification and Differential Diagnosis of Anemias Based on the Detailed Examination of over 200 Patients and a Study of the Literature EDWIN E. OSGOOD and HOWARD D. HASKINS	1367
1377	A Comparative Study of the Use of Whole Liver, Liver Extract and Ven-triculin HUGO A. FREUND and ALVIN E. PRICE	1377
1384	Raynaud's Disease Affecting Men EDGAR V. ALLEN and GEORGE E. BROWN	1384
1387	Does Liver Therapy Benefit the Diabetic? ELMER L. SEVINGHAUS	1387
1391	Primary Sclerosis of the Pulmonary Artery Report of a Case EDGAR R. FUND and THOMAS B. PRINIZY	1391
1397	Gonorrheal Endocarditis Summary of the Literature and Report of a Case ARTHUR M. HOFFMAN and FLOYD C. TAGGART	1397
1404	The Significance of Lymphatic Tissue and Adenoma-like Areas in the Thyroid Gland L. R. HIMMELBERGER	1404
1421	Pulmonary Lesions in Human Tularemia Pathological Review and Re-port of a Fatal Case STAIGE D. BLACKFORD	1421
1427	Oliver Goldsmith, M. D. LOUIS H. RODDIS	1427
1437	Editorial	1437
1440	Abstracts	1440
1442	Reviews	1442
1445	College News Notes	1445

NUMBER 12, JUNE, 1932

1447	An Experimental Basis for Intravenous Vaccine Therapy in Chronic Arthritis with a Summary of Results Obtained in Patients B J CLAWSON and M. WETHERBY	1447
1462	Hypertension and Diabetes HENRY J. JOHN	1462
1487	The Fallacy of the Weighed Diet in the Treatment of Diabetes Mellitus HELMUTH ULRICH	1487
1492	Myxedema A Case Report HENRY B. GOTTEN	1492
1497	Hypothyroidism without Myxedema JOHN B. YOUNG and SAMUEL S. RIVEN	1497
1506	Ventricular Paoxysmal Tachycardia, with Report of a Case EDWARD W. HOLLINGSWORTH	1506
1513	Control of the Tick-Borne Diseases—Methods and Economics NOXON TOOMAY	1513
1526	The Etiology of Colds JOHN E. WALKER	1526
1532	A Layman Considers Migraine WALTER B. SHEPPARD	1532
1540	Presidential Address American College of Physicians S. MARK WHITE	1540
1552	Editorials	1552
1554	Abstracts	1554
1557	Reviews	1557
1560	College News Notes	1560
1581	Index	1581

appendix may vary in shape and position and may determine certain peculiarities in the clinical manifestations of the diseased appendix. It is evident, that many of the variations in shape, size and position of the appendix may be due entirely to embryological conditions, presenting in no manner evidence of inflammatory processes, and are entirely compatible with normal health. Furthermore, when chronic disease of the appendix actually does occur, it is a well recognized fact, that this often represents but a part of the disease of the entire digestive tract. Gastro-intestinal infections rarely occur as single lesions, but are usually multiple and such affections as chronic appendicitis, chronic cholecystitis and peptic ulcer are not uncommonly associated. Heyd, Killian, and MacNeal,¹ and, more recently, Deaver,² attribute the primary inflammation in most instances to the appendix from which extension takes place into the liver and finally into the gall bladder. The formation of peptic ulcer may also represent a stage in this process. Inasmuch, therefore, as chronic gastro-intestinal infections extend gradually throughout the entire digestive tract the symptoms must vary according to the sites most markedly involved in the infection as well as with their anatomical and physiological characteristics. It is evident that an organ with a small outlet like the appendix or a small duct like the gall bladder might produce more severe manifestations as a result of infection than a large organ such as the liver. A knowledge that these infections often involve numerous areas of the digestive tract simultaneously will not

infrequently explain the development of new symptoms or the persistence of old ones.

Inasmuch as the appendix is constituted with a small lumen, when undergoing chronic inflammatory changes it will necessarily have its function interfered with. The contents of the cecum will enter the appendix under these conditions and decomposition take place with damage to the muscular wall. This will finally lead to disturbances of the functions of the cecum and ileum with extension into the colon, frequently increased by the deforming complications due to adhesions.

In this connection the work of Rohdenberg³ is of interest. In a pathological study of a large number of chronic appendices, he noted that the first changes occur in the tip, consisting of round cell infiltration about the Meissner ganglia, which increases until the ganglia are completely buried in round cells. Fibrosis now takes place until the ganglia are enveloped in dense fibrous tissue. From these observations he concludes that so called chronic appendicitis is a productive inflammation originating as a lesion of the sympathetic nervous system, which is not restricted to the appendix alone but involves the splanchnic sympathetic nervous system in general. According to Rohdenberg, the nerve lesions would explain reflex gastric symptoms such as attacks of spasm in the gastro-intestinal tract and pain, as well as the frequent absence of relief following appendectomy.

In order to establish the presence of chronic appendicitis, advantage is usually taken of a roentgen ray study

This method of investigation is, however, so extremely delicate that many unsuspected findings, such as slight delay in emptying, varying shapes and obliteration of the lumen are frequently noted, which in themselves have but slight significance. The most constant x-ray findings of chronic appendicitis are tenderness over the region of the appendix, frequent changes in shape abnormal and fixed position. The tenderness which is produced over the visualized appendix when moved under the palpating hand is of considerable value, being far more important than the tenderness ordinarily noted over McBurney's point when palpating the abdomen. This sign is often present during the recurrent attacks but usually disappears in the interval. Changes in shape of the appendix due to kinking and fixation from adhesions which are usually classified as important roentgenological findings may, however, be of but slight clinical significance. Other remaining signs are of even less importance. Of these, attention must be directed to abnormal filling. There is as yet so marked a disagreement as to the significance of filling or nonfilling of the appendix, that this sign must be at present entirely disregarded.

Brown and Gaither¹ call attention in the visualization of the appendix to its changes in shape as well as to the pain produced on palpation under fluoroscopic investigation as important evidences of chronic appendicitis. They consider these findings, when taken into consideration with the clinical history, as well as subjective and objective findings of the greatest value in diagnosis.

Of indirect signs, disturbances of the ileum and cecum must be considered. Ileal and cecal stasis may be caused by adhesions arising from the appendix, but according to White,² are not always due to this condition and may occur also as the result of atony and ptosis of the bowel. Pyloric spasm is frequently noted, but is of slight diagnostic importance. The roentgen ray records, therefore, many changes which are in themselves of slight clinical significance. These signs can therefore be utilized only as confirmatory evidence of chronic appendicitis and must be considered of value only when taken into consideration with the clinical manifestations of the disease. However, the x-ray may be of considerable aid in diagnosis in eliminating the presence of other affections.

Further confusion has arisen in diagnosis due to pathological studies of the appendix itself. No less an observer than Aschoff has directed attention to the occurrence of chronic inflammatory changes in the appendix in three-quarters to four-fifths of all individuals in the sixth and seventh decades of life. On the other hand, these findings, valuable as they may be, are in themselves, not of sufficient evidence to indicate that all such lesions are necessarily associated with symptoms. As a matter of fact, an individual may continue on throughout life with changes of this type without manifesting any evidence of the slightest discomfort. Aschoff, as well as many others, maintains that all cases of chronic appendicitis occur as the result of former acute attacks, though it is difficult to obtain a history of this

condition in many instances. A patient may have forgotten a previous attack, for many of these occur during childhood, and are overlooked or may have been of so mild a type as to escape detection. On the other hand, Deaver is firmly convinced, that not all chronic appendices are the result of previous acute disease, but may be due to a low-grade intestinal infection. According to our experience, one should hesitate in arriving at the diagnosis of this affection without a previous history of an acute or of recurrent attacks.

The clinical signs of chronic appendicitis are rarely distinctive. The pain and tenderness in the right lower quadrant may be due to other causes and in most instances localizing symptoms are absent. The gastric symptoms noted so frequently, such as loss of appetite, fullness, acidity, regurgitation, nausea and vomiting are due to pylorospasm and are not infrequently observed in other affections, as for instance, in gall bladder disease, and are by no means characteristic of chronic appendiceal disease. On the other hand symptoms apparently caused by chronic changes in the appendix are in many instances not produced by this condition itself, but are often the result of a general constitutional asthenia not uncommonly associated with visceroposis, a mobile right colon, movable cecum, mucous colitis, or ileal stasis. At times they may even be due to peptic ulcer or gall bladder disease. Case⁶ has shown from a study of his patients, who continued to complain of right lower quadrant pain following appendectomy, that in a large number of these cases, the etiology was found to be in the pelvic colon and rectum.

Pelvic tumors, carcinoma, diverticulitis, hemorrhoids and enterospasm constituted the most common causes in his cases.

Carnett,⁷ has more recently demonstrated that patients affected with so-called chronic appendicitis are usually not the subjects of this condition, but of more or less generalized disturbances involving the digestive tract, as well as the abdominal wall. According to him, this affection is most commonly observed in constitutionally predisposed individuals and occurs most frequently in the asthenic or visceroprotic neurotic type. It is on this account, that removal of the so-called chronic appendix is often ineffective in affording relief from the symptoms.

According to Carnett, the most frequent cause of pain and tenderness in the right lower quadrant of the abdomen is not to be found in the abdomen itself, but in the abdominal wall. It is due most frequently according to him, to neuralgia and less often to chronic strain of the lumbar spine and sacro-iliac joints. The method suggested by Carnett of differentiating between intra-abdominal and parietal tenderness is based on palpation of the abdominal wall following alternate relaxation and contraction. "Tenderness which is elicited over relaxed muscles may be either parietal or intra-abdominal in origin. Tenderness present with relaxed muscles and absent with tensed muscles is due to a subparietal lesion, and its cause should be sought inside the abdomen. Tenderness which is found both when the muscles are relaxed and when they are voluntarily tensed is due to an anterior

parietal lesion and its cause should be sought outside the abdominal cavity”

Carnett demonstrates the parietal location of the pain by determining tenderness “(1) by pinching abdominal skin and fat, (2) on finger-end poking of the abdominal wall, while the patient holds his abdominal muscles tense either by forcible contraction of the diaphragm or by raising and holding his heels above the bed with knees extended, (3) on making pressure over intercostal nerve trunks, and (4) on pinching or exciting finger-end pressure over Poupait’s ligament and over the upper posterior buttock region on the right side” In order to obtain the best results, Carnett advises that these tests be carried out with considerable force. Since we have been utilizing the method of examination as advised by Carnett, it is surprising to note, how many suspected cases of so-called chronic appendicitis are found actually to be due to extra-visceral disease. In his studies Carnett rejects completely the theory of Head, Mackenzie and others of the visceroparietal reflex which, according to him, has resulted in numerous errors in diagnosis and ineffective operations.

It is evident, that the diagnosis of so-called chronic appendicitis is fraught with considerable difficulty and should be arrived at only following a careful intensive study. It is also doubtful whether this condition can actually occur except when preceded by an acute attack.

Inasmuch as the only definite direct evidence of chronic appendicitis from a clinical standpoint is in the complete relief afforded following the therapeutic test—appendectomy, it becomes a

matter of extreme difficulty to estimate the actual incidence of this affection. According to our observations, which are largely in accord with those of Bettman,⁸ this must be far less than has ordinarily been held.

On the other hand, however, Deaver² maintains that chronic appendicitis is just as much a distinct clinical entity as chronic peptic ulcer or chronic cholecystitis. Inasmuch as it occurs associated with practically all forms of abdominal lesions, as for instance, chronic cholecystitis and chronic peptic ulcer, it must be regarded, according to him, as a factor of importance in the etiology of these affections. It is possible, that it is the original focus from which the infection extends. The fact that all patients who are operated on for chronic appendicitis are not relieved of all of their symptoms, by no means proves, according to Deaver, that no such entity exists. He is so strongly impressed with the necessity of removing every chronically diseased appendix or even a suspected one, that he considers it a grave error to expose the patient to the unjustifiable risk of not operating. For, according to him, even though the symptoms of which the patient complains are not overcome by this procedure, he is assured against future attacks as well as of complications.

In summing up the results of these observations, it is quite evident that conflicting views are still held regarding the clinical significance of so-called chronic appendicitis. While on the one hand, some maintain that this condition cannot be regarded as a definite clinical entity, others hold quite as firmly the contrary view. When one contem-

NUMBER 11, MAY, 1932

Rheumatic Heart Disease A Review. CLOUGH TURRILL BURNETT	1337
Early Manifestations of Rheumatic Infections in Young Children C C McLEAN	1357
Causes, Classification and Differential Diagnosis of Anemias Based on the Detailed Examination of over 200 Patients and a Study of the Literature EDWIN E OSGOOD and HOWARD D HASKINS	1367
A Comparative Study of the Use of Whole Liver, Liver Extract and Ventriculin HUGO A FREUND and ALVIN E PRICE	1377
Raynaud's Disease Affecting Men EDGAR V ALLEN and GEORGE E BROWN	1384
Does Liver Therapy Benefit the Diabetic? ELMER L SEVRINGHAUS	1387
Primary Sclerosis of the Pulmonary Artery Report of a Case. EDGAR R PUND and THOMAS B PHINIZY	1391
Gonorrheal Endocarditis Summary of the Literature and Report of a Case ARTHUR M HOFFMAN and FLOYD C TAGGART	1397
The Significance of Lymphatic Tissue and Adenoma-like Areas in the Thyroid Gland L R HIMMELBERGER	1404
Pulmonary Lesions in Human Tularemia Pathological Review and Report of a Fatal Case STAIGE D BLACKFORD	1421
Oliver Goldsmith, M D LOUIS H RODDIS	1427
Editorial	1437
Abstracts	1440
Reviews	1442
College News Notes	1445

NUMBER 12, JUNE, 1932

An Experimental Basis for Intravenous Vaccine Therapy in Chronic Arthritis with a Summary of Results Obtained in Patients B J CLAWSON and M WETHERBY	1447
Hypertension and Diabetes HENRY J JOHN	1462
The Fallacy of the Weighed Diet in the Treatment of Diabetes Mellitus HELMUTH ULRICH	1487
Myxedema A Case Report HENRY B GOTTEN	1492
Hypothyroidism without Myxedema JOHN B YOUNG and SAMUEL S. RIVEN	1497
Ventricular Paroxysmal Tachycardia, with Report of a Case EDWARD W HOLLINGSWORTH	1506
Control of the Tick-Borne Diseases—Methods and Economics NOXON TOOMRY	1513
The Etiology of Colds JOHN E WALKER	1526
A Layman Considers Migraine WALTER B SHEPPARD	1532
Presidential Address American College of Physicians S MARX WHITE	1540
Editorials	1552
Abstracts	1554
Reviews	1557
College News Notes	1560
Index	1581

The Clinical Significance of So-Called Chronic Appendicitis*†

By JULIUS FRIDINWALD, M D, F A C P, and THEODORE H MORRISON,
M D, F A C P, *Baltimore, Maryland*

MANY conflicting views concerning the significance of chronic appendicitis have been held during the past 10 to 15 years. While some clinicians have attributed many disturbances occurring in the abdomen to this cause, others have held that it in itself has but slight clinical significance. According to the latter conception, so-called chronic appendicitis is not a disease in which the symptoms are due entirely to the appendix alone, but one in which many other abdominal as well as other factors play an important rôle.

It is a well recognized fact, that since the advent of roentgenology numerous variations in the size, shape and position of the appendix have been observed, which have been recorded as chronic changes in this organ. In a considerable number of these reports, great significance has been attached to these findings as a probable cause of many digestive symptoms. Operation has been frequently undertaken upon the basis of

this observation alone. As the result of this procedure, namely, appendectomy, unfavorable outcomes have been recorded in many instances. These failures have led to a further study of this subject. As a result the McBurney incision has now ordinarily been discarded, and other abdominal disturbances have often been observed as the cause of the symptoms.

If the embryology of the appendix is carefully studied, the cause of many errors in diagnosis becomes apparent. This organ is derived from the cecum as a pouch about the seventh or eighth week of fetal life. The cecum occupies a high position under the liver during early development but descends lower later and drags the appendix down with it. The appendix finally assumes its position in the right iliac fossa, but the attachment to the cecum may vary markedly. In 90 per cent of instances, according to Tieves, it occupies a medioposterior position. The direction of the appendix is determined by the position of the attachment as well as the length of the mesoappendix. It may be directed posterior or lateral to the cecum and colon or into the pelvis beneath the terminal ileum or upward in the direction of the gall bladder. The meso-

*From the Gastro-Enterological Clinic of the Department of Medicine, University of Maryland.

†Delivered at the Baltimore Meeting of the American College of Physicians, March 23, 1931.

plates the many instances in which so-called chronic appendices have been removed without affording even the slightest relief on the one hand, and many others in which symptoms have occurred for years followed by almost immediate as well as permanent relief by this procedure on the other, the cause of the conflicting views concerning the significance of this condition becomes apparent. It is quite evident, therefore, that it is impossible to draw general conclusions, but that each case must be considered individually and only following prolonged and most careful study can final conclusions be arrived at leading to the proper method of procedure to be undertaken.

Finally, it must be held in mind that distress in the right lower quadrant alone is in itself by no means sufficient evidence as an indication for operation, and that unless there is a direct history of preceding acute attacks, doubt as to diagnosis must be maintained unless the other factors present point overwhelmingly in favor of this procedure. In a study of 100 cases in which appendectomies had been performed for so-called chronic appendicitis with unsuccessful results, the following diagnoses were finally established:

	No of Cases
Peptic Ulcer	24
Cholecystitis and Cholelithiasis	21
Renal and Ureteral Disease	4
Pelvic Disease	2
Colitis	11
Neuralgia of the Abdominal Wall	14
Carcinoma of the Cecum	2
Tuberculosis of the Cecum	1
Abdominal Adhesions	19
Hernia	2
—	—
Total	100

The following brief case reports may be of interest as indicating mistaken diagnosis as to so-called chronic appendicitis.

Case 1 Male, aged 27, digestive disturbance for years with abdominal colic, right lower quadrant discomfort and tenderness, diagnosis of chronic appendicitis, appendectomy performed, no relief, finally, complete recovery after treatment for mucous colitis, which evidently had been present for years.

Case 2 Female, aged 39, attacks of right-sided abdominal discomfort for years, beginning after birth of first child and occurring at irregular intervals, no discomfort or indigestion during intervals, tenderness in lower right abdomen, diagnosis of chronic appendicitis, McBurney incision, Chronic appendix removed, return of discomfort, three months' pain, gradually more violent, extending into upper right quadrant, diagnosis cholelithiasis, second operation, gall bladder removed filled with stones, complete recovery.

Case 3 Male, aged 25 years, indigestion for years, discomfort several hours after meals, usually relieved by food and alkalis, acid eructations, lower right discomfort and tenderness, diagnosis of chronic appendicitis with reflex stomach disturbance. Operation appendectomy, relief for one year, return of symptoms, more intense, gastric hemorrhage, tarry stools, x-ray confirmed diagnosis of pyloric ulcer, medical treatment, complete recovery.

Case 4 Male, aged 56, frequent attacks of lower right-sided pains for years, always some discomfort in this region, tenderness in the lower right quadrant, slight urinary discomfort, urine found normal, operation, chronic appendix removed, no relief, severe attacks of pain in six months, bloody urine, cystoscopic examination revealed ureteral stone near bladder, removed intravesically, complete recovery.

Case 5 Male, aged 44, right-sided pain for years with tenderness in that region, flatulency, eructations, fullness and pain following meals, relief in the recumbent posture, diagnosis, chronic appendicitis, appen-

dectomy, no relief, small epigastric hernia discovered after years second operation, repair of hernia, complete relief

On the other hand the following cases illustrate the great value of appendectomy in certain instances of chronic appendicitis

Case 1 Male, aged 19, discomfort in lower right quadrant of a mild type for years, indigestion with pressure, fullness following meals, eructations, flatulency, occasional nausea, loss of flesh, loss of appetite weak, nervous, unable to work, tenderness constantly in right lower quadrant, no definite history of former acute attacks, appendectomy, entire relief of symptoms, gradual recovery from weakness; gain of 20 pounds after three months, complete and lasting recovery

Case 2 Female aged 31, lower right quadrant pain for years with tenderness in this area, movable right kidney, pain more intense at menstrual periods, occasionally pain violent, requiring morphia for relief, various diagnoses made, ovarian disease, ureteral stricture, renal colic, many ureteral dilatations without relief, finally appendectomy performed, a chronic appendix removed, complete restoration of health

Case 3 Male, aged 51, affected with lower right-sided pain for years, never free from discomfort, no history of acute or recurrent attacks, tenderness over McBurney's point, appendectomy advised, unwilling to submit to procedure, sudden violent fulminating attack after 5 years, immediate operation, appendix removed revealing evidence of chronic inflammatory changes and gangrenous tip, many adhesions, stormy recovery, complete relief

Case 4 Female, aged 26, indigestion for years, pain in stomach occurring two hours following meals, relieved by food and alkalis, acid eructations, slight tender epigastric area occasional discomfort and tenderness in the lower right quadrant, test meal revealed hyperchlorhydria, x-ray showed small defect at pylorus and lower right quadrant adhesions, thorough ulcer treatment instituted, no relief, discomfort

in lower right abdomen more intense, tenderness in this region, appendectomy performed, curled up appendix removed contained concretions, complete recovery both from local and dyspeptic symptoms

Case 5 Female, aged 41, discomfort in right side for many years, occasionally colicky in type, tenderness in this region, never fever, considerable mucus discharged in stools in the form of shreds and bands, severe constipation, diagnosis mucous colitis, various treatment instituted, irrigations of many varieties, temporary relief only, tenderness in right side more intense, appendectomy advised, a chronic appendix with many adhesions removed complete recovery from discomfort, no further evidence of mucous colitis

CONCLUSIONS

From a careful review of the literature as well as from our observations extending over a large series of cases the following conclusions seem justified

1 Chronic appendicitis when considered purely from a clinical standpoint is not as is usually held. That it does, however, occur is evidenced by the complete and permanent relief at times afforded by means of appendectomy

2 The symptoms produced by so-called chronic appendicitis usually occur as (1) the result of either widespread disturbance involving other abdominal organs not limited to the appendix itself or as (2) forms of neuralgia occurring in the abdominal wall. The method of examination as advised by Carnett should always be followed in differentiating these conditions

3 The roentgen ray signs are usually misleading and difficult of interpretation, and can therefore be regarded as of minor significance only

4 Individualization is of paramount importance. The diagnosis should

never be made except following prolonged intensive study of the patient and should always be regarded with

suspicion unless a history of preceding acute or recurring attacks can be elicited

REFERENCES

- ¹HEYD, KILLIAN and MACNEAL The Liver and Its Relation to Chronic Abdominal Infection—Beaumont Foundation Lecture Course, 111, 1924
- ²DEAVER A J M Sciences, 177 749, 1929
- ³ROHDENBERG Arch of Path and Lab Med, 3 947, 1927
- ⁴BROWN and GAITHER South Med Jour 23 591, 1930
- ⁵WHITE Boston Med and Surg J, 188 387, 1923, and Amer J Roent and Rad Therapy, 13 18, 1925
- ⁶CASE Northwest Medicine, 20 165, 1921
- ⁷CARNETT Surg Gyn and Obst, 42 625, 1926
- A J M Sciences, 174 579, 1927
- A J M Sciences, 174 833, 1927
- J A M A, 91 1679, 1928
- ⁸BETTMAN J A M A, 83 1216, 1924
- Annals Int Med 2 516, 1928

Early Diagnosis of Neoplasms of the Digestive Tract*

By THOMAS R. BROWN, M.D., F.A.C.P., *Baltimore, Maryland*

I THINK we will all agree that the final aim of Medicine is the prevention or cure of disease—that our studies in gross and microscopic pathology, in bacteriology and in the ever-widening fields of biochemistry and biophysics have this as their ultimate goal. The age of therapeutic nihilism is past, we are no longer satisfied with etiology, pathology and diagnosis, therapy, be it psychical or physical, dietetic, pharmaceutical or surgical, is at last the *ultima thule* for which we are striving.

Perhaps there is no group of diseases in which therapy has been so bitterly disappointing as the malignant new growths of the digestive tract—for in this field relatively early diagnosis is essential if there is to be any chance of success of surgical removal—our *only* effective means of treatment at the present writing and it was but a few years ago that one of the masters in gastro-enterology, Boas, said, "No one can make an early diagnosis of digestive cancer—one must be satisfied with a correct *late* diagnosis."

In a sense this is true for there must be a period of latency, symptom-free, in the evolution of every neoplasm

when diagnosis is impossible except by the veniest accident. On the other hand the more we have studied these cases—and they have been the cause of our intensive study ever since the founding of our Clinic eighteen years ago—the more we are convinced that a relatively early diagnosis is possible in many cases, antedating by months, and sometimes by a year or more, the time when the diagnosis had been finally made, and that in many cases it was this fatal delay that spelled the difference between hopelessness and potential success.

Cancer is met with more frequently in the digestive tract than anywhere else in the body, it is definitely on the increase, an increase not to be explained by better methods of diagnosis or by the steady increase of the average age of man, but a true increase apparently due in some way to the accidents and incidents peculiar to an increasingly complex civilization. Is it due to new forms of trauma? Is it in any way due to increasing mental and nervous strain? Does our modern diet play a rôle? No one can prove that it does and yet Hoffman has found marked infrequency of digestive cancer among the primitive tribes of South America, McGarrison meets with practically no cases in the 400 to 500

*Delivered at the Baltimore Meeting of the American College of Physicians, March 23, 1931.

abdominal operations that he has performed yearly on the natives of the hills of Northern India, and Lane is firmly convinced that excessive consumption of meat, especially pork, and lessening intake of raw and rough foods with its inevitable lessening of motor activity of the large intestine, play a major rôle in the etiology of neoplasms of the digestive tract

But to the vast majority of students in this field, no satisfactory explanation has been found for its cause or its increase. Why is it so much more prevalent in some countries than in others? Is it contagious? May there be a hereditary factor? The work of Wells and Slye on white mice suggests this possibility and recent statistical studies, notably those of Wassinnck from Norway, are hard to interpret otherwise

Again, there is considerable evidence that in other parts of the body trauma plays a causative rôle, as, for example, the neoplasm of cotton-spinners and chimney sweeps, of workers in certain aniline dyes and tar, those due to parasites such as *Bilharzia*, *Schistosoma* and the *Spiroptera neoplastica*, and the skin cancers after exposure to the x-rays. There is, however, no evidence that metabolic disturbances or lack of vitamins play any part in its etiology

But none of these facts or factors are of any help to us in diagnosing digestive carcinomata and we must depend on other means of attack. We do not know its cause and therefore we have no means of preventing its development, and so our hope lies in a relatively early diagnosis and early and bold surgery

Cancer of the *oesophagus* should be ideal for surgical treatment were it not for the great technical difficulties involved. Diagnosis is made early. Progressive difficulty of swallowing in the middle aged or old should always make us suspicious, while oesophagoscopy and x-ray studies will usually confirm the diagnosis. It must not be forgotten, however, that intermittent dysphagia such as is usually met with in oesophagospasm occasionally occurs in new growths as well and must be ruled out by similar methods and by other means, notably the much less degree of oesophageal dilatation in the case of cancer

These cases give early symptoms, they develop slowly and metastasize late, they are simply waiting for a technique for successful removal. Robert Miller has performed successful oesophagectomies on dogs, but in the cases in which he and others have operated on human beings, all have succumbed to mediastinal infection. And yet, I know the time of their successful removal lies in the very near future. One has but to remember the almost insuperable technical difficulties that have been so brilliantly overcome in brain and thoracic surgery, fields that seemed equally hopeless but a short time ago, to feel that it is but a question of time before the skill and persistence of our surgical brethren will conquer this field as well. Until then, palliative treatment is all that we can employ, for radium and x-ray therapy and treatment with colloid metals have all proven woefully disappointing

In the case of new growths of the *stomach* the problem is essentially different, removal, successful complete

removal is possible, but to make this possibility a reality, early diagnosis is essential. In making this early or if you will, relatively early diagnosis—for the life span of gastric cancer is possibly *not* the usually accepted one-half to one and a half years but from one to three or four years and what we regard as the first act is in reality the second or third—the history of the case is of more importance than any or all other factors, for after all, unless we suspect, we will not thoroughly investigate.

In an analysis of all our cases of gastric carcinoma for a period of fifteen years less than 5 per cent gave a previous history suggesting ulcer, about 10 per cent had had previous vague gastric symptoms, 85 per cent had had absolutely *no* previous digestive symptoms and it must be this fact—this development *de novo* of digestive symptoms, usually but not always in persons of middle or later life, coming on with no obvious cause and not yielding to symptomatic treatment—that at the present writing at least is our one most valuable means of suspecting or diagnosing gastric cancer and in making us pursue those intensive studies—gastric contents for dropping acid or achlorhydria with special studies as to the soluble protein contents, stool for occult blood, radiography and, especially, repeated and careful fluoroscopy—which in most cases should give us our diagnosis and tell us whether we are dealing with cancer or with one of those conditions with which it is most likely to be confused, chronic biliary tract disease, gastric lues atypical ulcer or pernicious anemia. The tragedy of gastric can-

cer is that its seat of election is not pylorus or cardia, but in the vast majority of cases the lesser curvature, the silent area, where it may grow for a surprising length of time and reach a very considerable size before producing symptoms sufficient to make the patient consult his physician. These symptoms are in no wise characteristic or even suggestive in themselves—usually a slight loss of appetite, some discomfort or fulness, sometimes pain, occasionally slight nausea, in other words those of an ordinary banal dyspepsia—but, and this is the crux of the matter, appearing without cause and *not* disappearing under appropriate symptomatic treatment.

In that very small group of ulcers developing into cancer, 5 per cent in our series, only 11 per cent and 34 per cent in the last two large German series, a *lessening* of appetite, a dropping of acid, persistence of occult blood in the stool, should arouse our suspicion.

It is quite impossible to tell from the size of the growth or the length of the history whether it is operable. Some metastasize early and these are obviously hopeless, a few grow to a considerable size and still remain a local problem only, but obviously in all cases the chance of success depends upon the earliness of diagnosis. I am more and more convinced that it is wiser to operate on a well-grounded suspicion than to wait for a diagnosis beyond criticism. At present we have had more than 50 cases in which surgery seemed justifiable and in about one-half of these the results were promising, one case living fifteen years, several more than ten years and the

rest from two to five years after the operation. We have had no success with any other form of therapy, radium, x-ray, colloid lead, colloid selenium. Incidentally, none of our cases, however extensive the gastric resection, has developed a blood picture suggesting that of pernicious anemia, these results agreeing with those of Henschel of Basle in 77 cases of subtotal gastrectomy.

In new growths of the *small intestine* it is practically impossible to make an early diagnosis, for with the liquid contents and its rapid passage, signs of obstruction must come late, and even then are difficult to recognize—pain, gaseous distention, delay of the barium column, distension of the gut with gas above a definite point as seen in the fluoroscope.

Fortunately the condition is extremely rare—Rankin and Mayo had only 31 cases from 1919 to 1929 at the Mayo Clinic, while in this same ten year period, there were 2,775 cases of cancer of the large bowel and 2,646 of the stomach. The relative lateness of the diagnosis was shown by the fact that whatever the operation, no patient lived more than three years and the average duration of life after the operation was less than one year.

On the other hand, in the case of cancer of the *large bowel*, we have our best opportunity of combining early diagnosis and potential surgical cure, for here we have semi-solid intestinal contents, a much slower passage, a short well defined tube and obviously much earlier and more easily localized obstructive or ulcerative phenomena, while our means of confirming the diagnosis are much more exact.

And yet, a few years ago, I had 9 consecutive cases incorrectly diagnosed, cases with symptoms lasting from six to eighteen months and wrongly diagnosed as mucous colitis, intestinal neurosis, chronic constipation or gastric dyspepsia, for, just as in rare cases of gastric cancer, the symptoms may be entirely intestinal, so in a few cases of intestinal neoplasm, the predominant symptoms are gastric. But, in every one of these cases, malignancy should have been suspected almost from the very first for in every case the symptoms represented various manifestations of large intestinal obstruction, progressive or intermittent, and in every case the symptoms came out of a clear sky with *no* previous intestinal symptoms, in every case the diagnosis could have been anticipated by many months if, and this is essential, the possible cause had been suspected and simple confirmatory methods used—careful abdominal palpation, in a hot bath if the wall is rigid, study of the stool for occult blood and pus, digital rectal and sigmoidoscopic and proctoscopic examinations and very careful X-ray studies, especially fluoroscopy with the barium enema and ruling out by the proper methods tuberculosis, lues, ulcerative colitis, polyp and post-operative adhesions. A persistent filling defect, persistent occult blood in the stool, although obviously it is better, although not often possible, to make the diagnosis before ulceration is present, sometimes a palpable tumor, these with the local and general symptoms, must and usually can give us our correct diagnosis.

From our intensive clinical studies in this field for nearly twenty years, we are convinced

First that there is no test, no laboratory technical method, that is as valuable in diagnosing gastro-intestinal neoplasms as a careful analysis of the history of the case—discarding no symptom because it may seem insignificant. It is upon the art, not the science of medicine, that we must lean, that nice balancing of the facts, that keen judgment in their interpretation, that careful weighing of cause and effect, in other words those highly developed qualities that spell the real clinician. With this as our foundation, we can make a surprising number of relatively early diagnosis if we utilize in addition all the other means at our command, especially careful palpation, the study of gastric contents and stool, the use of instruments for direct study and the x-ray, especially fluoroscopy.

Second, at the present writing surgery, radical surgery, offers our *only* hope of cure, but to make this possible or probable early diagnosis is essential. It is far wiser to explore on a well grounded suspicion than to wait for an absolute diagnosis when all too often metastasis and extension of the growth makes complete surgical removal impossible.

But after all, it is not upon the shoulders of the consultant, the specialist or the surgeon that the responsibility for making the early diagnosis of digestive neoplasms lies, but upon those of that great body of internists and general practitioners to whom the patients come first with their symptoms—symptoms rarely characteristic, often very mild, usually simulating simple functional disturbances in their early phases—but in the majority of cases having one quality in common, one motif that runs through this dance of death, that there had been no history of previous digestive disturbances, that they appeared without apparent cause, that they did not yield quickly to symptomatic treatment. It is this development *de novo*, this progression irrespective of treatment that should arouse our suspicion as to possible malignancy and that should make us utilize every scientific method at our command to confirm or refute this possibility. This, and this only, seems to me at the present writing to be our only possibility of making an early diagnosis, and with this early diagnosis or probability, of materially diminishing the appalling mortality and of appreciably increasing our percentage of permanent cures by the only successful mode of treatment—early, bold, radical surgery.

Studies on the Mechanism of the Pain of Peptic Ulcer*†

By FRED M. SMITH, M.D., F.A.C.P., and W. D. PAUL, M.D., *Iowa City, Iowa*

VARIOUS explanations have been given for the pain of peptic ulcer. In general, however, there are two prevailing conceptions. One is primarily concerned with the irritating action of the hydrochloric acid of the gastric juice on the exposed nerve endings in the ulcer. The other places the emphasis on the altered motor function as represented by spasm, particularly of the pylorus or pyloric sphincter, hyperperistalsis or a combination of these factors producing increased gastric tension.

Palma¹ was one of the first to study the mechanism of gastric pain by the introduction of acid into the stomach. Bonninger,² Heinecke and von Selms³ reported the reproduction of the pain of gastric ulcer by the administration of varying strengths of hydrochloric acid, whereas, in normal individuals, the results were negative. Sippy,⁴ later championed the acid theory of the production of the pain in peptic ulcer. He furthermore believed that the corrosive action of the acid interfered with the healing of the ulcer which

was the basis for the alkali therapy in his well known treatment.

Palmer⁵ has more recently investigated the influence of acid on the pain of peptic ulcer. He administered through a Rehfuess tube, 200 cc of a 0.5 per cent hydrochloric acid. If the pain was not reproduced within thirty minutes, another 200 cc was added. The same amount was occasionally administered the third time. The results are tabulated in three groups. The first is concerned with normal individuals in whom the results were uniformly negative. The second pertains to the study of twenty-five patients with ulcer in whom the typical distress was not induced. Only four of these were said to be in a "distress period." He defines a "distress free period" as one in which spontaneous pain was not experienced during the twenty-four hours preceding the test. The last group deals with eighty-four cases in which the pain was induced by the administration of the acid. In this series the distress was reproduced in 324 of the 404 attempts. Seventy of the eighty failures occurred during the distress free period. It is evident, from the above results, that unless the pain is occurring at frequent intervals, it is not possible to induce it by the

*From the Department of Internal Medicine, State University of Iowa.

†Delivered at the Baltimore Meeting of The American College of Physicians, March 23, 1931.

repeated administration of 200 cc of 0.5 per cent hydrochloric acid

The roentgenological examination in peptic ulcer directed attention to the possibility of spasm and hyperperistalsis contributing to the production of the pain. Hurst^c was one of the first to emphasize the importance of increased gastric tension in the production of the distress. He concluded, from an experimental and clinical study that the mucous membrane of the stomach is insensitive to stimulation from dilute hydrochloric acid and dilute organic acids. He, furthermore, stated that the surface of a gastric or duodenal ulcer is no more sensitive to tactile, thermal and chemical stimulation than the intact mucous membrane. This investigator⁷ has more recently described in detail his conception of the mechanism of the pain in peptic ulcer. He first considers duodenal ulcer and attributes the distress to an increase in the intragastric tension of the pyloric vestibule. In brief, he explains the increased tension on the basis of an achalasia or a spasm of the pyloric sphincter interfering with the expression of the gastric contents into the duodenum and the approach of an active peristaltic wave which is sufficiently powerful to obliterate the lumen of the pyloric section. He considers that the mechanism in gastric ulcer is the same as that in duodenal ulcer. In the gastric ulcer located some distance from the pylorus the function of the pyloric sphincter may not be disturbed. In these instances, however, the author points out that a spasm of the circular muscle of the segment of the stomach corresponding to the ulcer may be of sufficient in-

tensity to produce pain when approached by an active peristaltic wave. Ryle⁸ in a consideration of the nature of visceral pain, has stressed the importance of increased tension in the wall of the viscus.

The work of Carlson⁹ on the hunger contraction stimulated an investigation of this feature in connection with the pain of peptic ulcer. Ginsburg, Tumpowsky and Hamburger,¹⁰ Carlson¹¹ and Hardt,^{12, 13} employing the balloon method, observed that the pain in gastric and duodenal ulcer was synchronous with the occurrence of strong contraction waves. These contraction waves corresponded with the hunger contraction waves described by Carlson in the normal individual. These investigators were not able to correlate the appearance of the pain with the gastric acidity. Hardt¹³ reports the study of a patient with gastric ulcer in whom no free acid was demonstrated by repeated aspiration of the gastric contents. In this patient, the typical pain, in almost every instance, occurred with the registration of a peristaltic wave. The results of Ortmayer¹⁴ and Homans¹⁵ neither confirmed nor disproved the above observation. In their work, however, the balloon was probably well above the most active portion of the stomach.

Poulton¹⁶ reports the reproduction of the typical distress in patients with peptic ulcer by the introduction of air into the stomach. Immediate relief was obtained by aspirating the air. In this connection, the observations of MacLeod¹⁷ are of interest. An Eimhorn tube was introduced into the first portion of the duodenum in twenty cases of duodenal ulcer. The position

of the tube was verified by fluoroscopic examination. Air was administered and the typical pain reproduced. In each instance, the diagnosis was confirmed by operation. Poulton,¹⁸ later studied visceral pain by means of a balloon in the lower end of the esophagus. He concluded that pain may be induced by increased tone alone, but pointed out that the latter feature was usually accompanied by a hyperperistalsis.

Reynolds and McClure¹⁹ investigated, by fluoroscopic method, the relation of the gastric motor phenomena to the pain of peptic ulcer. They were invariably able to demonstrate these features during periods of distress. A similar method was employed by Wilson²⁰ in the study of the pain of duodenal ulcer. In thirteen of sixteen cases, the pain terminated abruptly upon filling the duodenal cap by manual pressure.

In a previous investigation,²¹ the recurring localized epigastric distress associated with irritable colon and chronic appendicitis was demonstrated to be gastric in origin. This distress, which may have all the characteristic features of that of peptic ulcer, was accompanied by an increase in tone and an active peristalsis of the pyloric section of the stomach. These alterations in the gastric activity were induced by a reflex stimulation from the colon and appendix. They were abolished and the pain eliminated by the administration of atropine.

A reflex stimulation of the stomach from the colon was demonstrated in certain instances of peptic ulcer. This was accompanied by an epigastric distress which was said to be identical

to that attributed to the ulcer. The gastric alterations were similar to those associated with irritable colon and chronic appendicitis, and the pain occurred under the same condition.

The above investigation led to the study of the changes in tone and the peristaltic activity of the pyloric region of the stomach in peptic ulcer. It was believed that a more accurate knowledge of the altered gastric phenomena in this particular section of the stomach would contribute to the explanation of the pain, and possibly point to a more satisfactory method of treatment. The present report is concerned with the mechanism of the pain.

METHOD

The method was similar to that employed in the former investigation. A small rubber balloon was passed into the pyloric section of the stomach and anchored in this location by an Einhorn bucket. This balloon was connected through a water and air system with a bellows tambour which recorded the gastric activity on a kymograph. A Rehfuess tube was usually introduced into the stomach with the balloon and acid determinations made during the registration of the gastric activity.

FINDINGS

The records taken during the active stage of ulcer showed recurring periods of increased gastric activity in which an increase in the tone and spasm of the pyloric section were prominent features. The record in Figure 1 was taken of a patient with gastric ulcer soon after admission to the hospital. Early in the record, there is a violent tone change with the on-

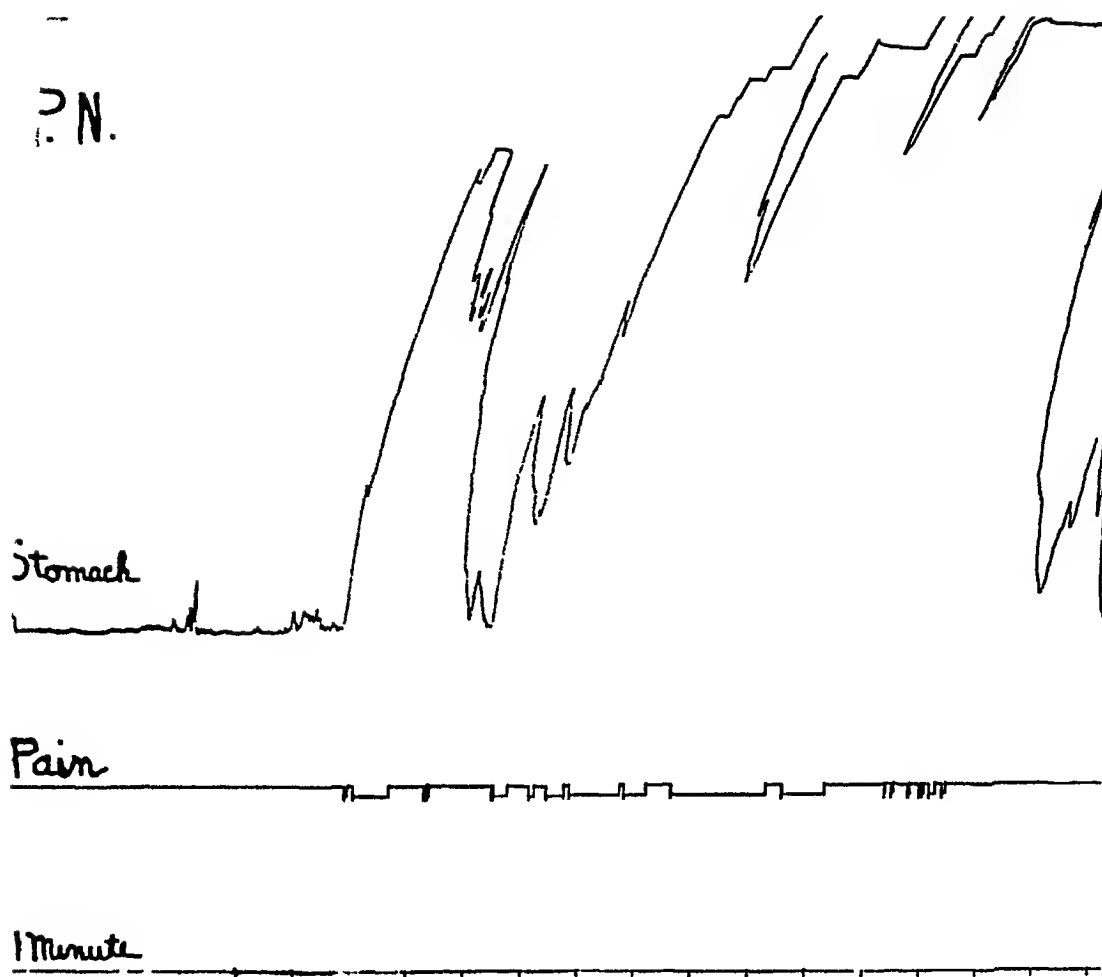


FIG 1

set of an active peristalsis. This was accompanied by the onset of severe epigastric distress and marked rigidity of the upper abdomen. The pain finally became so intense that the operator was alarmed for fear that there might be a perforation. Following the withdrawal of the balloon, however, there was immediate relief from the pain.

The record in Figure 2 represents a continuous registration of the gastric activity of a patient with duodenal ulcer from 9 30 A M to 1 P M. There

were three periods of active peristalsis which were accompanied by a marked increase in tone. Each of these lasted about thirty minutes and two were accompanied by pain. The first occurred between 9 30 and 10 30 A M. It terminated abruptly and the patient went to sleep. He was awakened about 11 A M soon after the onset of the second paroxysm, by a sharp pain. Following the termination of the second period of exaggerated gastric activity, which was similar to the first, the stomach was relatively inactive until

EF
1/20/30

Small



Outline

Outline
of 30m

10 30m



Outline of 30m

Outline

11 30m

10 30m

Outline of 30m
10 30m

istalsis intensified the distress. It is assumed that the sudden termination resulted from the escape of gas through the relaxation of the pyloric sphincter by the atropine.

COMMENT

In the above series of experiments, the gastric alterations were similar during periods of pain. These changes were characterized by an increase in tone and the onset of an active peristalsis. The pain in each instance corresponded with the passage of a peristaltic wave except in the more severe form when there was an apparent persistent spasm of the pylorus (Figure 1). These findings are in accord with the observations of Ginsburg, Tumpowsky and Hamburger, Carlson and Hardt. While a hyperperistalsis invariably accompanied a significant increase in tone, the latter feature was apparently fundamental to the production of the pain. It will be noted that the terminations of the paroxysm of increased gastric activity were likewise similar, regardless of the agent responsible. In some instances, the termination was spontaneous, while in others, it promptly followed belching, vomiting, the aspiration of air, or the administration of atropine. These observations support the contention of Hurst and Ryle, that the pain is primarily dependent on an increase in the intragastric tension. The roentgenological findings of Wilson, in the study of the pain of duodenal ulcer may be explained on this basis. It will be recalled that the pain terminated abruptly upon filling the duodenal cap by manual pressure. It might thus be argued that the pain was relieved by the re-

duction in the intragastric tension from expressing the gastric contents into the duodenum.

The significance of the observation of Poulton on the occurrence of typical ulcer pain following the introduction of air into the stomach is more apparent in view of our results. In the experiments in Figures 4 and 5, the paroxysms of increased gastric activity accompanied by pain were induced by the administration of air and terminated by the reduction in the intragastric tension. The experiment in Figure 6 is of particular interest in this connection. It would seem probable that the gas formed from the administration of the sodium bicarbonate was responsible for the increased gastric activity.

CONCLUSIONS

These findings are very similar to the gastric alteration associated with irritable colon and chronic appendicitis, and the pain occurred under the same condition. In the former study, it was not believed that the hydrochloric acid of the gastric contents was a factor in the production of the distress, and in the present investigation, there was no apparent correlation in these features. The pain in each may be relieved by various agents as alkalis, food, belching, aspiration of air, vomiting and the administration of atropine. It would thus seem that the production of the pain is primarily dependent on the altered motor phenomena and the associated increased gastric tension. We wish, however, to investigate other measures commonly employed in the treatment of the pain of peptic ulcer before coming to a more

definite conclusion At the same time, the influence of the administration of a more detailed study will be made of hydrochloric acid.

REFERENCES

- ¹TALMA, S Zur Behandlung von Magenkrankheiten, Zeit f klin Med, 1884, VIII, 407
- ²BONNIGER, M Zur Diagnose des Ulcus Ventriculi, Berl klin Wchnschr, 1908, XLV, 396
- ³HEINEKE, D, and VAN SELMS, M De la sensibilité de l'estomac, Arch des Mal de l'Appar dig, 1908, II, 467
- ⁴SIPPY, B W Oxford Medicine, New York, Oxford Univ Press, Vol 3, Page 132
- ⁵PALMER, W L. The mechanism of pain in gastric and duodenal ulcer, production of pain by means of chemical irritants, Arch Int Med, 1926, XXXVIII, 694
- ⁶HURST, A F The sensibility of the alimentary canal, London, 1911
- ⁷HURST, A F, and STEWART, M J Gastric and duodenal ulcer, New York, Oxford Univ Press, 1929
- ⁸RYLE, J A A clinical study of pain with special reference to the pains of visceral disease, Brit Med Jour, 1928, I, 537
- ⁹CARLSON, A J The control of hunger in health and disease, Chicago, 1906
- ¹⁰GINSBURG, H, TUMPOWSKY, I, and HAMBURGER, W W Newer interpretation of the gastric pain in chronic ulcer, J A M A, 1916, LXVII, 990
- ¹¹CARLSON, A J Contributions to the physiology of the stomach, XLIV The origin of the epigastric pains in cases of gastric and duodenal ulcer, Amer Jour Physiol, 1917, XLV, 81
- ¹²HARDT, LEO L J Pain in active pathologic processes in stomach or duodenum, gastric and duodenal contractions as the direct cause J A M A, 1918, LXX, 837
- ¹³HARDT, LEO L J. Studies of the cause of pain in gastric and duodenal ulcers, peristalsis as direct cause of pain in gastric ulcers with achylia and in duodenal ulcers, Arch Int Med, 1922, XXIX, 684
- ¹⁴ORTMAYER, MARIE Gastric motor activity in patients with peptic ulcer, Arch Int Med, 1925, XXXV, 423
- ¹⁵HOMANS, JOHN The relation of pain in gastric and duodenal ulcer to muscular activity of the stomach, Amer Jour Med Sci, 1919, CLVII, 74
- ¹⁶POULTON, E P An investigation of the cause and relief of pain in gastric ulcer, Lancet, 1921, CC, 263
- ¹⁷MACLEOD, DONALD A note on pain in relation to duodenal ulcer, Lancet, 1929, CCXVII, 1358
- ¹⁸POULTON, E P On an experimental study of certain visceral sensations, Lancet, 1928, CCXV, 1223
- ¹⁹REYNOLDS, L, and McCLURE, C W Motor phenomena occurring in normal stomachs, in presence of peptic ulcer and its pain, as observed fluoroscopically, Arch Int Med, 1922, XXIX, 1
- ²⁰WILSON, MALCOLM, J Duodenal ulcer Observations on the behavior of stomach and duodenum in the presence of pain, Arch Int Med 1928, XLI, 633
- ²¹SMITH, F M, PAUL, W D, and FOWLER, W M The mechanism of the epigastric distress associated with an irritable colon and chronic appendicitis, Arch Int Med 1931, XLVII, 316

Rheumatoid Arthritis*

By RUSSELL L. CECIL, M D , *New York City*

RHEUMATOID arthritis might well be called the step-child of Medicine for the reason that, like some other chronic diseases, it has always received scant attention from both investigators and practitioners. Osler himself is quoted as having remarked that when an arthritic patient walked into his consultation room, he always had a strong inclination to jump out the window. Most of the research work on arthritis has been spasmodic or accidental, and until recent times few practitioners have made a special study of the disease.

It is unfortunate that such a common malady should have received this neglect. Within the last few years, however, a noticeable change has taken place in the attitude of medical men toward rheumatic diseases, and because of this intensive study and research, definite knowledge is being gained concerning the various types of arthritis and the modes of treatment. For one thing we have learned to classify arthritic conditions into various groups. Both European and American students are agreed that most cases fall into one or the other of two main divisions, infectious or rheumatoid arthritis, and hypertrophic or osteoarthritis.

Osteoarthritis is something that all

of us achieve as the reward of old age, though it may appear in the early fifties, particularly in stout women who have just passed through menopause. There is no reason to believe that osteoarthritis is an infection, on the contrary, it appears to be a phase of senescence brought about by insufficient blood supply to the joint structures. The small capillaries become thickened and occluded, and as a result certain degenerative changes occur in the bone and cartilage. A classic example of osteoarthritis is furnished by the so-called Heberden's nodes on the distal phalangeal joints of the fingers.

Rheumatoid arthritis is a true inflammatory process characterized in the early stages by migratory pain and swelling in various joints and in the late stages by ankylosis and deformity. For twenty years rheumatoid arthritis has been looked upon by most students of the disease as a chronic infection, though the exact nature of the infection has not been disclosed. There are several features of the disease which strongly support the infectious theory: its almost constant association with foci of infection, the moderate fever and leukocytosis which occur in some cases, the loss of weight and secondary anemia, the complications such as iritis, pleuritis and pericarditis, and finally its similarity in the early stages to gonococcal arthritis and rheumatic fe-

*Presented before the Baltimore Meeting of The American College of Physicians, March 23rd, 1931

ver all suggest an infectious origin. The pathological findings are also those of a chronic infection. The granulation tissue which develops in the joint cavity and which if not checked, eventually fuses the articular surfaces together, can hardly be imagined as being derived from any other source than a bacterial one. The adhesions which one sees in these joints differ in no respect from the adhesions in the peritoneal and pleural cavities resulting from bacterial infection.

Bacteriologists have made extensive efforts to solve the riddle of rheumatoid arthritis, but their results have been inconsistent and desultory. To be sure, some form of streptococcus has long been suspected of being the etiological agent, chiefly because streptococci are frequently present in the original foci of infection, but efforts to isolate streptococci from the blood and joints have been either entirely unsuccessful or only partially so.

Moon and Edwards,¹ Richards,² Billings³ and his co-workers, and Hadjopoulos and Burbank⁴ have all reported the isolation of streptococci from the blood or joints or from both sources in a certain number of cases of rheumatoid arthritis, the percentage of positive cultures, however, being comparatively small. More recently Forkner, Shands and Poston⁵ have reported cultures from the joints in 63 cases of chronic infectious arthritis with the isolation of streptococci in 11, or 17 per cent. of the cases. In a series of papers published during the last two years from the medical department of Cornell University, the writer, in collaboration with Edith E. Nicholls and Wendell J. Stainsby,^{6,7}

has described a method of culturing the blood and joints in rheumatoid arthritis and also in rheumatic fever, which has proven remarkably satisfactory in respect to the isolation of streptococci. The basis for successful cultivation of these streptococci appears to rest, first, on very carefully and specially prepared culture media, and second, on observation of these cultures over a period of two to four weeks of incubation. Altogether 154 cases of rheumatoid arthritis have been subjected to blood cultures by this method. Of these cases 49 were also subjected to joint cultures. Of the 154 patients who had blood cultures, 96 or 62.3 per cent, yielded a streptococcus. In several patients a streptococcus was obtained from the blood in two or even three successive cultures.

As a control on these findings, 104 individuals either normal or suffering from some condition other than rheumatoid arthritis, were subjected to blood cultures, the technic being similar in all respects to that used on patients with rheumatoid arthritis. Of these controls 20 were normal healthy individuals with no joint symptoms and no obvious foci of infection. The remainder of the control group were patients suffering from some disease. Of these 23 were middle-aged patients, who presented a typical picture of degenerative arthritis with hypertrophic changes in the bones. The blood cultures on all this group were sterile. The remaining 61 controls were patients suffering from various diseases, including infections of various kinds. Of these 61 patients, 4 showed streptococcus viridans in their blood cultures. The four positive controls pre-

sented certain features in common, three had active foci of infection of the type usually associated with arthritis, while the fourth was an acute respiratory infection. In this connection it is interesting to note that there have been several reports in the literature lately on isolation of streptococci from the bloodstream of patients with acute respiratory infections.

In 40 cases of rheumatoid arthritis cultures were made from one of the affected joints. In 33 cases (67.3 per cent) a short-chained streptococcus was recovered from the joint cultures. In 48 cases that were subjected to both blood cultures and joint cultures, 37 (77 per cent) showed a streptococcus in either the blood or the affected joint. Control joint cultures were made on 18 patients who were suffering from conditions other than rheumatoid arthritis. The joint cultures from these 18 controls all remained sterile.

Time does not permit a detailed description of these streptococci which have been recovered from the blood and joints of rheumatoid patients. Suffice to say that both cultural and immunological evidence supports the conclusion that they are atypical hemolytic streptococci. They possess a remarkable capacity, however, for losing their hemolytic quality when kept for some time on laboratory culture media. They are quite different in their cultural and biological characteristics from the streptococci which we recover from the blood and joints of patients with rheumatic fever. In the latter disease cultures have usually yielded green streptococci, which tend to fall into a number of biological groups.

Even more significant perhaps than the presence of streptococci in the

blood of rheumatoid patients are the specific streptococcal agglutinins which these patients show in their blood sera. These agglutinins have been recently described in a publication from our clinic, and their presence has already been corroborated by Dawson, Olmstead and Boots⁸ who, because of these agglutinins, advance the theory that rheumatoid arthritis is a streptococcus hemolyticus infection. They look upon the joint manifestations, however, as allergic or toxic in character. These streptococcal agglutinins are so definite in a high percentage of cases that they can be made of considerable practical value in the diagnosis of this form of arthritis. In perfectly typical cases, such a test is perhaps not necessary except where the titer of the agglutinins is to be followed as an index of treatment, but in very early cases or in mixed forms of arthritis, or particularly in obscure back conditions, the agglutination test has proved of great value in our arthritis clinic in the correct classification of cases. In routine clinic work we have largely abandoned blood and joint cultures because they are difficult and time-consuming, and prefer the agglutination reaction both for diagnosis and prognosis. As a rule the more advanced the arthritis, the more potent the agglutination reaction. The agglutinin titer in rheumatoid arthritis usually runs between 1:320 and 1:5120 or even higher. Every patient with arthritis now admitted to the Cornell Arthritis Clinic is subjected to an agglutination test and a sedimentation test. Both of these tests are extremely valuable in differential diagnosis and both are of value in guidance of therapy.

When arthritic strains of streptococci are injected intravenously into rabbits, a faithful reproduction of rheumatoid arthritis is produced in these animals. Streptococci are recovered from the blood and joints of the arthritic rabbits and their blood contains agglutinins similar in all respects to the agglutinins found in the blood of human patients. The problem of reproducing rheumatoid arthritis in animals is a large one and so far only the surface has been scratched in our work at Cornell. We hope to go into this problem more thoroughly in the future.

It is only fair in this connection to report that the results obtained from bacteriological study of rheumatoid arthritis in other clinics have not always been consistent with our own. Nye and Waxelbaum⁹ were unable to corroborate our results in either rheumatic fever or rheumatoid arthritis. Dawson, Olmstead and Boots¹⁰ have obtained only negative results from blood and joint cultures in rheumatoid arthritis. Margolis and Dorsey¹¹ of the Mayo Clinic have partially corroborated our findings in that in a total of 29 specimens of either bone or synovial membrane from patients with infectious arthritis, 6 yielded streptococci on culture, and 5 diphtheroid bacilli. The most complete corroboration of our findings has come from Gray and Gowen,¹² who have recently published their results on blood and joint cultures in rheumatoid arthritis. In a series of 37 cases of rheumatoid arthritis, a streptococcus of the arthritic type was recovered in 67.6 per cent of the cases, a proportion almost identical with that obtained by us. Gray and Gowen have also noted that the organism produced

partial hemolysis on blood agar. Swift¹³ at the Rockefeller Institute obtained streptococci in only a small percentage of his patients with rheumatic fever, but Dr. William H. Park¹⁴ and his co-workers in the research laboratories of the New York City Department of Health are recovering green streptococci from both the blood and joints in a very high percentage of rheumatic fever cases.

This inconsistency in results is of course disappointing, but I believe can be explained on the basis of some slight differences in culture media. That such differences do exist is proved by the fact that even when cultures of our streptococci are sent to some laboratories, the local bacteriologist is at times unable to cultivate the organism on his own culture media.

Some investigators who have not been successful in cultivating streptococci from the blood and joints of patients with rheumatoid arthritis and rheumatic fever have advanced the theory that the streptococci which we have recovered are not actually in the blood or joints, but are contaminations from the skin or air. This theory, however, is hardly valid because

- 1 Streptococci are rarely encountered as contaminants in bacteriologic work. In our own laboratory we have repeatedly exposed plates for several hours at a time, but have never recovered streptococci from them.

- 2 If these streptococci were contaminants one would expect to find just as high an incidence of positive cultures in the controls as in the arthritic series. Such, however, was not the case.

- 3 In almost 50 per cent of the positive cultures, both blood culture flasks

yielded streptococci, a finding entirely inconsistent with the contamination theory.

4 The high titer of specific streptococcal agglutinins in the blood and joint fluids of arthritic patients speaks strongly for the presence of these streptococci in the tissues themselves and also for their pathogenic quality. The fact that the agglutinins tend to disappear as the patient recovers is also significant.

Perhaps the most important practical phase of the newer bacteriology of rheumatoid arthritis is its bearing on vaccine therapy. Vaccine therapy has no doubt been considerably abused in some quarters, and for this reason has come into disfavor with many physicians as a therapeutic agent. This applies to arthritis as well as to other acute and chronic infections. However, in allergic conditions such as bacterial asthma and certain skin conditions, vaccines have come to be a part of the standard treatment, and recently Swift has published favorable reports on the use of streptococcus vaccine in the treatment of rheumatic fever, in which allergy seems to play an important part.

We have presented evidence to show that rheumatoid arthritis is a chronic specific infection caused by a special strain of streptococcus hemolyticus. If further study confirms this theory, it is most natural that efforts toward the development of some form of specific therapy should be undertaken with this organism. During the past three years we have treated several hundred rheumatoid patients with a streptococcus vaccine prepared from our "typical strain." We hope some time in the near future to report in detail our

results with this form of therapy. At present I can do no more than give the impressions obtained from three years of experience with this agent. The vaccine was originally prepared in the usual manner, that is, by killing washed cultures at 60° C and standardizing by the Wright method. More recently, however, the streptococci have been killed by formalin instead of by heat, and this method seems to have produced a vaccine of higher antigenic power. At present we are administering vaccine by both the subcutaneous and intravenous methods using doses of from 100,000,000 to 1,000,000,000 in the former, and from 100,000 to 1,000,000 in the latter. In both methods we try to avoid unpleasant reactions. The interval between injections is four to five days, occasionally a week. In trying to evaluate vaccine therapy in arthritis, one must take into consideration the part which improved personal hygiene and the removal of any foci of infection may play in a patient's recovery. Other forms of therapy, such as medication, physiotherapy, hydrotherapy, etc., must also be given some weight, but unfortunately, in our experience, this is not considerable.

The results which we have obtained with vaccine therapy in the treatment of rheumatoid arthritis may be divided roughly into three groups. 1 Patients who make complete recovery from all joint symptoms. These patients for the most part have had a mild form of arthritis, but some could be classified as moderately severe. 2 Patients who make considerable improvement, but eventually reach a stationary stage and do not recover completely. These are

usually patients who have had arthritis for several years, with well-marked joint symptoms 3 Patients who show little or no effect from vaccine therapy These are usually patients of long-standing, with well-marked or advanced joint symptoms There are exceptions to all these groups I can recall some early cases that have not responded to vaccine therapy, but on the other hand I can recall some almost hopeless patients who have made surprising improvement with practically no other treatment than rest and vaccine In each of the three groups there have been many patients who, in addition to the vaccine treatment,

have had foci of infection removed; but there are many others whose treatment consisted of vaccines alone

On the whole, we may say that after having started out with considerable misgivings as to the value of streptococcus vaccine in the treatment of this disease, we have been forced to take the opposite position, and we now consider streptococcus vaccine an important therapeutic agent in the treatment of rheumatoid arthritis Just how much of the benefit obtained is referable to specific effect and how much to foreign protein effect is a problem which can be settled only by further study

REFERENCES

- ¹MOON, V H, and EDWARDS, S H Results of Blood Cultures in Rheumatoid Arthritis, *J Infect Dis*, 1917, 21 154
- ²RICHARDS, J H Bacteriologic Studies in Chronic Arthritis and Chorea, *J Bacteriol*, 1920, 5 511
- ³BILLINGS, F, COLEMAN, G H, and HIBBS, W G Chronic Infectious Arthritis Statistical Report with End-Results, *J A M A*, (April 15) 1922, 78 1097
- ⁴HANJOPOULOS, I G, and BURBANK, R A Preliminary Study Bearing on the Specific Causative Factors of Multiple Infective Arthritis, *J Bone and Joint Surg*, (April) 1927, 9 278
- ⁵FORANER, C E, SHANDS, A R, and POSTON, M A Synovial Fluid in Chronic Arthritis, *Arch Int Med*, (Nov) 1928, 42 675
- ⁶CFCU, R L, NICHOLLS, E E, and STAINSBY, W J The Bacteriology of the Blood and Joints in Chronic Infectious Arthritis, *Arch Int Med*, (May) 1929 13 571
Bacteriology of the Blood and Joints in Rheumatic Fever, *J Exper Med* (Nov) 1929, 50 617
- ⁷CECIL, R L, NICHOLLS, E E, and STAINSBY, W J The Etiology of Rheumatoid Arthritis, *Amer J Med Sci*, (Jan) 1931, 181 12
- ⁸DAWSON, M H, OLMSTEAD, M and BOORS, R H Studies on Etiology of Rheumatoid Arthritis II Agglutination Reactions with Hemolytic Streptococci in Rheumatoid Arthritis, *Proc Soc for Exper Biol and Med*, 1931, 28 421
- ⁹NYR, R N, and WAXELBAUM, E A Streptococci in Infectious Arthritis and Rheumatic Fever, *J Exper Med* (Dec) 1930, 52 885
- ¹⁰DAWSON, M H, OLMSTEAD, M, and BOORS, R H Studies on the Etiology of Rheumatoid Arthritis I Bacteriological Investigations on Blood, Synovial Fluid and Subcutaneous Nodules in Rheumatoid Arthritis, *Proc Soc for Exper Biol and Med*, 1931, 28 419
- ¹¹MARGOLIS, H M, and DORSEY, A H E Chronic Arthritis Bacteriology of Affected Tissues, *Arch Int Med* (July) 1930, 46 121
- ¹²GRAY, J W, and GOWLN, C H A Bacteriologic Study of Chronic Infectious Arthritis, *J Med Soc of N J*, 1931
- ¹³SWIFT, H F, and KINSILLA, R A *Arch Int Med*, (March) 1917, 19 381
- ¹⁴PARK, W H By personal communication

A Diagnostic Triad in Syphilitic Aortitis*†

By C S DANZER, M D , F A C P , Brooklyn, N Y

IT is superfluous to discuss the importance of recognizing aortic syphilis early. The contrasting results in properly treated and untreated cases speak for themselves. As far as I know, a clean-cut symptom-picture by which this disease may be diagnosed, is still lacking. I shall attempt this task in the present communication.

The confusion in the past was due largely to two factors, the frequent association of this disease with aortic atherosclerosis, and the misinterpretation of the Wassermann reaction.

How often have we seen on examining an aorta at autopsy, atheromatous, calcified plaques with wrinkling of the intima and pink streaks in the depressions between the folds! The commonly accepted diagnostic criteria, consisting of a dilated aorta, a systolic aortic murmur and a ringing aortic second sound are frequently due to co-existing aortic sclerosis with or without hypertension, rather than aortic syphilis. I have observed narrow or normal aortas without the signs just enumerated, in well-defined syphilitic

mesaortitis, as the following case will show.

G H, a 40 year old male, who denied venereal infection, consulted me on February 28, 1929, because of severe *angina* after effort, excitement or meals, during the past year. It was especially severe in cold weather or when his stomach was full. He had observed that eating rare beef was apt to be followed by anginal pains. In the past 6 months he experienced abdominal pain and bloating after meals and excessive flatus. When the latter was expelled, the *angina* lessened. He slept badly because of exciting dreams which in turn induced *angina*, dyspnea and an indescribable "fright" over the precordium. These exhausted him, so that he had to get out of bed and stand in order to relieve the *angina*. Digitalis aggravated the *angina*.

Physical examination was essentially negative, no aortic murmurs, nor accentuation of the A₂ over the aorta. Only in the supra-clavicular fossa (over the subclavian artery) was the A₂ intensified. B P 110/60, pulse varied from 54 to 64 and the heart sounds were feeble. E K G Diphasic T in lead I. *The width of the aorta was normal on x-ray* (6 ft plate). Only a slight knuckling on the left border could be seen. The blood Wassermanns done with the usual technique using both alcohol and cholesterol antigens and the Kolmer modification were strongly positive, the Kahn test reacted similarly.

The other significant features in this case were the negative vagus (carotid sinus) reflex and the increased blood sedimentation reaction. These points will be elaborated later. Suffice it here to say that

The carotid sinus reflex was negative on the left side and doubtful on the right

*From the Medical Services of the Cumberland and Unity Hospitals, Brooklyn, N Y

†Read before the Minneapolis Meeting of the American College of Physicians, February 14th, 1930

CAROTID SINUS REFLEX

Pulse Beats per 10 second Period

	Right side	Left side
Before test	10	10
During test	8	10
After test	10	10

The blood sedimentation reaction with the Westergren method was 41 mm per hour (normal 4-6 mm) and 106 for 24 hours (normal 40-60) After 8½ months of treatment (bismuth, mercury, salvarsan, iodides) the sedimentation rate was reduced to 6 mm per hour and 68 mm per 24 hours The Wassermann tests still showed a 3 plus reaction, but after a course of bismarsen, the Wassermann and Kahn tests became negative and all the clinical symptoms disappeared (October 1, 1930)

The Wassermann has at times misled me False positive reactions, especially with cholesterin antigens, are not rare in cases of aortic atheromatosis In such cases, a wide aorta, a bruit, or ringing A2 sound may easily be ascribed to luetic aortitis The conversion of a positive into a negative complement-fixation test after provocative salvarsan injections, the correlation with other serological reactions (Kolmer method, alcoholic antigen, and Kahn test) will reduce this source of error The following case will illustrate the point under discussion

A S (case No 236403), a man, 59 years old, came to the Medical Center complaining of recurrent anginal pains on exertion or after eating He got no relief from nitroglycerin Three months before he developed symptoms of acute obstruction of the left coronary artery This was verified by the existence of a negative T wave in lead I and a notched R in all the leads of the electrocardiogram X-ray disclosed calcification and knobbing of the aorta, and moderate cardiac (especially left ventricular) enlargement The cardiothoracic ratio was 54% The B P was low 104/70, and the heart sounds were audible Blood Wassermann on

December 11, 1929, showed a 3 plus reaction with the cholesterin antigen, negative with the alcoholic The same result was obtained on repetition of the tests a week later He was given 2 doses of neo-salvarsan (3 Gm) a week apart On January 14 and 20 the Wassermann tests with both antigens gave a negative reaction The Kahn test was also negative This man was obviously suffering from coronary and aortic sclerosis, not due to syphilis

On the other hand a person with a negative Wassermann and none of the conventional signs of aortic disease may have aortic lues In such instances, repetition of the blood examination after provocative measures, spinal fluid examination, the therapeutic test and the clinical picture to be described in this paper, will generally settle the diagnosis

T D, (case No 240534), an obese, ruddy, 65 year old man came to the Medical Center on January 16, 1930, complaining of anginal pain on exertion or after meals for the past 12 years Of late these had become quite severe and at times were accompanied by typical "angor mortis" He had a wide tortuous aorta, 65 cm in diameter, moderate inaudible heart sounds with negative T waves in all leads of EKG, small pupils which reacted to light, normal tendon reflexes, and a negative Wassermann with both alcoholic extract and cholesterin antigens Thirty-five years ago he had a chancre which was untreated Despite the results of the Wassermann test, it seemed plausible that the man had latent syphilis with localization in the aorta With this thought in mind, the patient was given a course of iodides The Wassermann reaction (end of March, 1930) gave a 2 plus reaction with an alcoholic antigen

Syphilitic mesoaortitis has in many cases a characteristic symptom triad consisting of angina pectoris, a negative carotid sinus reflex, and a rapid blood sedimentation rate A positive

Wassermann occurs in two-thirds of the cases of luetic aortitis and serves only as a confirmatory test. Dilatation of the aorta, insufficiency of the aortic valve, a murmur and a ringing A2 sound may, but need not, be present. It is most commonly a disease of the fifth decade of life. The following two cases are presented in order to emphasize the diagnostic triad.

K R, a woman 45 years old, who had never born children but had one miscarriage, came on May 1, 1929, complaining of burning anginal pain during the past year. It radiated down the arms and to the teeth and came on especially on walking out of doors, uphill, or during cold weather. When she leaned forward, she experienced more pain in the sternum. The chest pain was compared to that of swallowing a hot potato. She had no knowledge of a luetic infection. A diagnosis of hypertension was made a year before.

The patient was obese (about 50 lbs overweight) with a Corrigan pulse, 64 per minute, B P 185/70, hemoglobin 57 per cent and a normal urine. Over the cardiac base a to-and-fro murmur was heard, and the diastolic bruit was transmitted to the apex. The aorta was wide, and dynamic pulsations were seen on the fluoroscopic screen. The E K G showed a left ventricular preponderance with no T wave changes.

The carotid sinus reflex was negative on both sides.

CAROTID SINUS REFLEX		
Pulse Beats per 10 second Period		
	Right side	Left side
Before test	11	11
During test	11	10
After test	11	11

The sedimentation rate was 53 mm per hour, 124 mm in 24 hours.

The Wassermann showed a 4 plus reaction with the various antigens and Kolmer technique.

Diagnosis *Luetic mesoaortitis complicated by aortic insufficiency.*

E B, a 36 year old police officer, experienced for 1½ years angina on exertion or after meals. Amyl nitrite gave him immediate relief. His angina increased steadily despite the reduction of weight from 225 to 185, brought on by dieting. Examination of his heart disclosed a loud rasping diastolic murmur over the entire precordium with a heaving apex beat. He had no edema of the legs. The B P was 105/60. The aorta was dark, wide and expansile and the left ventricle was markedly hypertrophied. The blood Wassermann was 4 plus. He was given 6 doses of salvarsan by his physician, Dr G, but developed chills and a temperature of 104° following the injections, so that they had to be discontinued.

Carotid sinus reflex was essentially negative.

CAROTID SINUS REFLEX		
Pulse Beats per 10 second Period		
	Right side	Left side
Before test	22	23
During test	20	20
After test	22	22

A diagnosis of *syphilitic mesaortitis with aortic insufficiency* was made and bismuth injections and iodides were advised. He improved remarkably for a while, attempted to perform the strenuous duties of his calling and the angina returned. He then consumed 135 tablets of nitroglycerin (gr 1/100) daily for 2 weeks, developed progressive heart failure and died.

A leading symptom of this disease is angina pectoris. The pain may be very severe especially in an hypersensitive person or absent in one insensitive to visceral pain. Between these extremes there are numerous transitional variations. The conventional steno-cardiac pain after exertion or eating is by no means invariable. It frequently comes at rest, during the night and, as I have observed rather frequently on bending forward.

The degree of response to painful stimuli may be roughly tested by ap-

plying deep pressure with the thumb to the styloid process (between the mastoid and the mandibular angle), a method introduced by E. Libman of New York. It should be done carefully by exerting equal pressure on both sides

A hypersensitive person says "it hurts," and draws the head away, the normal one says "it is just the pressure of your fingers", a hyposensitive individual says nothing when the test is made

If pressure against the styloid of one side is more painful, the anginal pain is usually felt on the homolateral side. In such cases pressure over the brachial plexus (Schmidt) or the eye (Bernstein) may also be more painful on the affected side.

In a hyposensitive person, anginal equivalents must be diligently looked for. These commonly consist of disagreeable sensations in the chest varying from anxiety to a premonition of impending death, usually though by no means always, after exertion. Sometimes the sensation is not even projected to the chest. It may consist of an unexplainable "feeling of nervousness."

As a general proposition one may expect to find a typical reaction when a normal or hypersensitive person develops aortic disease. This rule is not invariable as the next case will show.

I. K., a 47 year old, highly emotional Jew with a metabolic rate of plus 12 and bilateral hyperesthesia of the styloids and ocular bulbs, but no brachial hyperesthesia, developed progressively increasing palpitation on exertion, nocturnal attacks of asthma and nocturnal 1st years ago. Several weeks before examination he suffered a severe attack of vertigo and vascular collapse. His

physician, Dr. S., found him with a cold clammy skin and later the systolic B P was 210. Ever since then his chief trouble has been palpitation on exertion, *paroxysms of nocturnal dyspnea and heaviness in the chest, but without acute pain*. After careful questioning he admits only one attack of pain in the precordium and left arm.

Examination. He had a dark, wide aorta and a slightly enlarged heart on x-ray. A delayed systolic murmur, a loud A2 over the aorta and a short systolic blow at the apex were heard. B P 183/105. *Carotid sinus reflex was strongly positive*, especially on the right side.

CAROTID SINUS REFLEX

Pulse Beat per 10 second Period	Right side Left side	
Before test	20	19
During test	14	16
After test	20	19

On February 20 a soft diastolic puff was heard to the inner side of the apex. Was this an aortic insufficiency? If so it would argue strongly for the luetic origin of the angina. A blood sedimentation reaction was done and found *decreased* ($3\frac{1}{2}$ mm per hour, 60 mm in 24 hours) and the carotid sinus reflex was positive. This *eliminated*, to my mind, the *diagnosis of syphilitic aortitis*, though his age was 47. The Wassermann on Feb 21 was negative and supported the diagnosis of aortic sclerosis.

This case illustrates the existence of coronary (aortic) disease in a nervous hypersensitive man, which induced, instead of anginal pain, palpitation on exertion and cardiac asthma. The absence of pain in coronary disease in a hypersensitive individual is perhaps the exception to the rule.

Alarming dreams may arouse the patient from sleep with a frightful but not painful precordial sensation and constitute another variation of the anginal symptom (L. Braun¹).

A hyposensitive person may have extensive coronary disease, even a fa-

tal coronary thrombosis without pain. In this category is the sudden and unexpected death after a formal dinner casually ascribed to "acute indigestion", or the apparently healthy man who is found dead in bed in the morning, or the painless death during sexual intercourse (*la morte douce*). People with reduced sensibility to pain are likewise apt to be the carriers of painless duodenal ulcers for years. Amidst good health a peritoneal perforation or a severe hemorrhage discloses the presence of the treacherous lesion.

It behooves us, therefore, in hyp-sensitive people, to regard minor chest symptoms or simple indigestion seriously and to look for organic disease in the heart or abdomen. It is plain that the estimation of the reaction to pain should be frequently practiced.

The next sign in the triad which merits discussion, is the negative "carotid sinus reflex" (Hering). At the Boston meeting of the American College of Physicians in April, 1929, I reported the occurrence of a positive reaction in non-syphilitic coronary angina. The case L. K., just described, illustrates this point. In luetic aortitis with angina on the other hand, the reflex is generally negative. In order to clarify these remarks it will be necessary to review briefly the physiology and clinical application of this reflex.

It is elicited by pressing the thumb over the common carotid artery at the level of the thyroid cartilage. At this point the vessel bifurcates into its internal and external branches and a slight bulging of the artery called "carotid sinus" may be felt. The heart rate is counted for 10 seconds, then the sinus is compressed against the

firm tissues of the neck for 10 seconds and the cardiac frequency is again determined. Similar counts are made for the following two 10 second periods. The reflex is positive if there is a distinct slowing during the carotid compression.

This is the old vagus pressure phenomenon described by Czermak,³ who thought it due to the mechanical stimulation of the efferent vagus fibers in the carotid sheath. His error has been pointed out by Hering⁴ who showed that even pinching the exposed vagus nerve, fails to slow the heart. On the other hand, light pressure with the finger on the skin over the carotid, a manipulation obviously insufficient to reach the deep position of the vagus, may cause cardiac standstill for 5 to 7

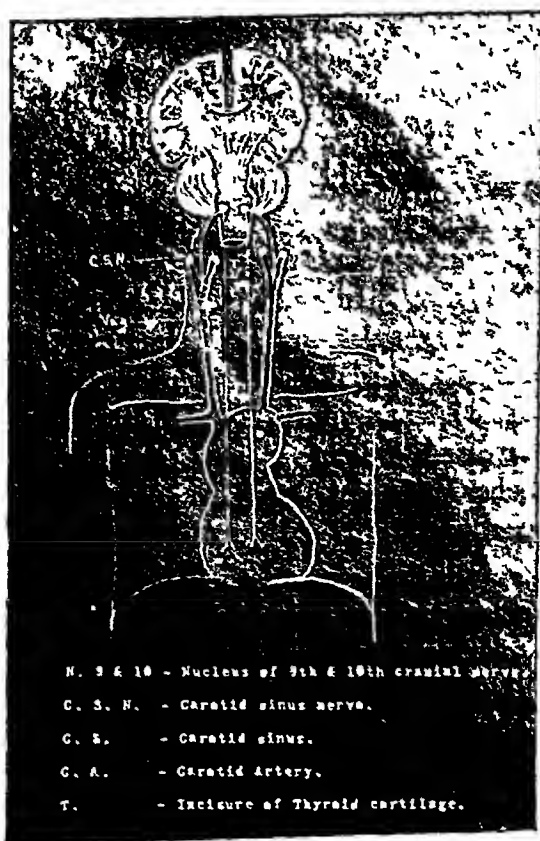


Fig 1

seconds I have observed such reactions many times

Hering proved that the afferent part of the reflex arc was formed by the so-called carotid sinus nerve, a small branch of the glosso-pharyngeal. The motor vagus fibers form the efferent segment of the arc. The reflex therefore starts from the carotid sinus and ends in the heart. The common nucleus of the 9th and 10th cranial nerves completes the arc.

Last year I suggested as a possible explanation for a positive reflex² an arteriosclerotic lesion at the carotid sinus. It has been shown by Chiari⁵ that this lesion occurs frequently in association with coronary arteriosclerosis. Monckeberg⁶ confirmed his findings and said that these lesions are the earliest localizations of the arteriosclerotic process and occur often in young adults or even children. Thus the reason for a positive vagus response in cases of coronary (and carotid sinus) sclerosis is evident.

The importance of applying this test to young people even without angina is obvious. In a recent address by Joslin⁷ the existence of premature and serious arterial disease (coronary sclerosis) in youthful diabetics was stressed. This is but one instance where the test may be applied to advantage.

A little light on the otherwise obscure pathogenesis of juvenile arteriosclerosis was furnished by the work of E. Wolfkoff⁸ who found nodular thickenings of the intima in the coronaries beginning in infancy. These, of course, are physiological reactions. In young adults (32-36 years) the thickness of the intima exceeds by several times

that of the media, especially near the origin of these vessels. The superimposition of atheromatous lesions on a partially stenosed coronary, might seriously interfere with the myocardial circulation and offer an explanation for the frequency of the symptoms of coronary obstruction even in young people.

The following case may illustrate how the carotid sinus reflex may help to recognize pathology in the coronary arteries before the onset of angina or other clinical symptoms.

C. R., a 57 year old, healthy-looking business man consulted me because of generalized pruritus for 3 to 4 weeks especially on coming from a cold into a warm room. He noticed that the palms of his hands perspired freely. Thirteen years ago he suffered from pruritus which recurred during the following 3 winters. He had no precordial pain nor dyspnea, and his B. P. was 145/85. His urine was negative until recently when a trace of albumin and a few hyaline and granular casts were found. The physical examination was essentially negative, except for a slightly ringing A₂ sound. The aorta under the fluoroscope was not dilated, but dark, the cardiac size was normal. Capillaroscopy showed a group of aneurismal and varicose capillaries in the skin near the nail-beds. Incidentally this was the anatomical substratum for his pruritus (cutaneous vasoneurosis). The blood sedimentation reaction was moderately increased.

CAROTID SINUS REFLEX

Pulse Beats per 10 second Period

	Right side	Left side
Before test	10	10
During test	5	10
After test	10	10

Positive reaction on right side

The presence of a positive carotid sinus reflex pointed to a sclerotic lesion of the right carotid and coronary arteries. The dark aorta and the ringing

A2 sound supported this diagnosis. This man had at the time of examination no cardiac symptoms, but on further inquiry, it was learned that he was rejected by an insurance company 11 years ago (age 46) for albuminuria and hypertension. Eight months after that, he was operated upon for a perinephric abscess, and 1½ years later his urine and blood pressure were found normal and he was accepted by the insurance company.

The positive carotid sinus reflex was the most significant sign of arteriosclerosis and dovetailed with the history of hypertension 11 years ago. He is probably in the *presymptomatic stage of coronary disease* at present. Further observation will be necessary in order to verify this hypothesis.

A positive carotid sinus reflex may therefore indicate coronary arteriosclerosis even before or without angina. Timely care of the heart and vessels may aid in prolonging life. In the case of *aortic syphilis*, this reflex is generally negative, carotid pressure fails to produce cardiac slowing. The reason for the negative reaction may be as follows. Syphilitic aortitis is generally unassociated with coronary closure or lesions at the carotid sinus unless complicated by atherosclerosis. Since such lesions are required to give a positive vagus reaction, its absence in aortic lues may be understood.

The third symptom is the rapid blood sedimentation rate. How can we explain this? It must be recalled that *syphilitic aortitis is an infectious process, aortic sclerosis is a degenerative one*. A fast sedimentation rate occurs chiefly in infectious conditions. It is however non-specific, occurs in

active infections, and is comparable to an increased leucocyte count. This test has been successfully used in following the progress of such infections as pulmonary tuberculosis, pelvic inflammations and syphilis. Active aortic lues is associated with a *fast sedimentation rate because it is an inflammatory disease*. Up to the writing of this paper, I have seen no case of active syphilitic aortitis without a rapid sedimentation reaction. For the performance of this test, the Westergren⁹ technique is recommended because of its simplicity.

The following case will serve to illustrate the error that may result from the misapplication of the carotid sinus and sedimentation reactions. In this patient, the *failure to sufficiently relax* the muscles of the neck to effectively compress the carotid artery, resulted in a negative response. At a later examination the patient relaxed better and a positive reaction was elicited on the right side. Another confusing feature in this patient was the fast sedimentation rate which was thought at first to indicate an active infection, perhaps syphilis. It was later accounted for by myocardial necrosis following coronary thrombosis. The latter condition, in my experience, is often the cause of rapid blood sedimentation. It is necessary, therefore, to insist upon the entire symptom triad for the diagnosis of syphilitic aortitis.

Case W J Y, 59 years old, suffered for the past 3 years from angina pectoris on exertion, particularly in cold weather or on walking against the wind. Postural dizziness, brachial paresthesia, anginal pain in the left arm, ear, face, and dyspnea on effort completed the picture. In the past year his symptoms had been quite severe,

though never as bad as during the month before examination. Since then he had been home and mostly in bed. The examination disclosed a muddy pallor of the face, the pupils reacted to light, the blood pressure was 135/85, sensibility to pain over the styloid was normal, the heart sounds were feeble and slightly irregular, the liver edge was a hand's breadth below the costal margin and over the left pulmonary base a number of râles were heard. He had no edema of the legs. The aorta was wide and the cardiac outline hazy on fluoroscopic examination. The lungs showed congestive hyperemia. Urine was negative except for a moderate increase in urobilinogen due to liver congestion.

The blood sedimentation reaction on two occasions gave a very fast rate, the first reading was 83 mm per hour, the next one 95 mm.

The carotid sinus reflex at the initial examination gave a negative response. It seemed at first that with a fast sedimentation rate, it might indicate syphilitic aortitis. On the second examination, however, though the blood sedimentation was still fast, the *carotid reflex* was distinctly *positive* on the right side, so that *for 4 seconds*, there was *complete cardiac standstill*.

We still had to explain the fast sedimentation. An electrocardiogram showed a negative or diaphasic T wave in leads 1 and 2 with a convexity of the ST interval, indicating a myocardial lesion of coronary obstruction. It was obvious, therefore, that the patient was undergoing myocardial necrosis which accelerated the blood sedimentation. Negative Wassermanns with the different antigens and techniques excluded the diagnosis of syphilis.

The sedimentation test is extremely valuable when used judiciously. It can, however, be very misleading as the following case will show.

H. G., male 58, consulted me on Sept 29, 1927, because of a vise-like constricting pain in the chest and abdomen after exertion in the past 8 days. Dyspnea was not present. Abdominal distension after meals and

nocturia had been present for 6 months. He was rejected by a life insurance company 6 months previously because of glycosuria.

He was a little man (Wt 109 lbs) with a grayish complexion and a B P 115/70, and his urine had only a trace of albumin. Eyes showed no arcus senilis. Heart. An irregularly intermittent rough systolic and a short diastolic murmur were heard over the entire precordium. On fluoroscopy a dilated aorta with a hypertrophic left ventricle were seen. There was no fever. A pericarditis was present, but its etiology was obscure. Was it rheumatic or epistemicardiac?

Two years later he returned with entirely different complaints. He had lost 15 lbs, felt weak, had a dragging sensation in the lower abdomen and dyspnea on exertion. His B P was 95/60, his hemoglobin 56 per cent and his stomach contents showed a subacidity. *His blood sedimentation was very fast*, 56 mm per hour and 127 mm in 24 hours. *Carotid sinus reflex was moderately positive on both sides*.

CAROTID SINUS REFLEX

Pulse Beats per 10 second Period	Right side Left side	
Before test	10	9
During test	7	6
After test	10	9

In view of the fast sedimentation reaction with angina the question of aortic syphilis arose. This diagnosis was excluded because the carotid reflex was positive and the Wassermann was negative. The diagnosis of coronary sclerosis is more likely and his pericarditis of two years ago was perhaps due to myocardial infarction.

To account for his sedimentation reaction one must assume either another infection or gastric subacidity. I have found the blood sedimentation increased in several cases of gastric subacidity. I fail to understand the reason, but offer it simply as an empiric

observation In this case, therefore, the subacidity of the stomach may stand in some relationship with the fast sedimentation

This case illustrates also the possibility of detecting coronary disease in the absence of anginal or other cardiac symptoms The loss of weight with its consequent reduction of the load on the heart, may be responsible for the disappearance of the anginal symptoms

With the help of the carotid sinus reflex, latent coronary disease may be recognized, even those who lose their stenocardiac symptoms, e.g., with the advent of cancerous or other forms of cachexia, may be diagnosed

We must insist therefore, that the "symptom triad" be used collectively, not singly A fast sedimentation reaction alone may be caused by infections, gastric anacidity, or myocardial necrosis

Mrs M J, 65, with a history of rheumatic endocarditis in her son and grandchildren, had been complaining in the past 15 months, of attacks of palpitation and throbbing in the head These started suddenly and ended more gradually They came frequently during the night and awakened her from sleep She also experienced palpitation and cold sweats on exertion but no dyspnea The first attacks came after an emotional bout The paroxysms of tachycardia kept the patient from sleeping The essential features in her examination were a markedly dilated aorta on fluoroscopic examination, moderate hypertension, 185/85, slight bilateral arcus senilis, pupils reacted to light, a loud diastolic decrescendo murmur over the entire precordium, and a short systolic murmur over the aorta The fingers showed a positive capillary pulse There was neither edema of the legs, nor congestion of the liver or lungs The knee jerks were normal and her hemoglobin 70 per cent

The carotid sinus reflex was negative In

view of this fact and the presence of a diastolic aortic murmur the thought of lues had to be considered The blood sedimentation reaction, however, on two occasions (one year apart) showed fairly normal figures, the first test gave an average of 8 mm, the second 15 mm per hour To exclude lues more thoroughly, Wassermann tests (including the Kolmer) were done The results were negative

A diastolic aortic murmur in a person with a wide expansile aorta, without a history of rheumatic infection, would be taken to indicate lues, despite the negative Wassermann The normal sedimentation rate, however, excluded active syphilitic disease Diagnosis Chronic rheumatic aortic insufficiency complicated by hypertension and paroxysmal tachycardia

To further illustrate how the knowledge of this symptom triad may be applied to clarify other apparent imponderables, a case of combined syphilitic and sclerotic aortic disease will be presented This diagnosis would be difficult with the usual clinical methods The necessity for such an attempt arises particularly in the indication for treatment, since active specific therapy applied to an uncomplicated case of atherosclerosis might react disastrously

M B, a 50 year old obese woman weighing 232 lbs, and only 5 ft in height, developed dyspnea and precordial pain on exertion 3 years ago One year later attacks of cardiac asthma followed by precordial pain during the night, came on In one of these paroxysms she felt as though she were dying The attacks would awaken her from sleep and compel her to sit in a chair with her legs hanging down in order to ease the breathing Urination occurred 2 to 3 times a night but was reduced during her asthmatic attacks The patient felt warm even in cold weather

A significant point in her family history is that out of 10 children only 3 are living, the rest died in infancy She had no spontaneous miscarriages however

Examination Pulse 96, respiration 46, deep, labored and noisy, B P 220/130, and the aorta was wide on fluoroscopy and percussion. On x-ray the lungs looked congested and hazy. The breathing was costal and the diaphragm was almost immobile during the attacks. She had a number of these in my office. During one of them, her breathing rose to 120, she was pale, perspired profusely and could not lie down. Heart sounds were loud, regular, with no murmurs, the rhythm at the apex was pendular. Lungs. A few submucous râles were heard over the lung roots, but not at the bases.

The urine contained albumin, and gave a 3 plus urobilinogen reaction, sugar was negative and specific gravity 1018. The Wassermann on the spinal fluid was 4 plus. The average blood sedimentation rate was 24 mm per hour.

The Hering reflex was positive on the right side.

CAROTID SINUS REFLEX

Pulse Beats per 10 second Period	Right side Left side	
Before test	15	15
During test	8	15
After test	15	15

Diagnosis Tertiary lues is undoubtedly present. The high infant mortality and the positive spinal fluid Wassermann bear this out. We cannot, however, explain the positive Hering reflex and the hypertension without the diagnosis of arteriosclerosis. This reflex, even by itself, suggests aortic or coronary sclerosis. Attacks of cardiac asthma in my experience are more commonly present in non-luetic than in specific vascular disease. Therefore the diagnosis of combined syphilitic and atherosclerotic aortic disease was made.

A practical clinical point in this case was the "feeling of warmth in the skin" that this patient experienced. The close connection between the calibre of the arteries and the warmth (rather than the color) of the skin, has been emphasized by the recent studies of Sir Thomas Lewis¹⁰. The

relation between peripheral vascular dilatation and cardiac asthma has been shown by Eppinger, Papp and Schwartz¹¹. According to them it is the removal of the normal resistance in the arterioles that permits the blood to surge through the periphery and overwhelm the heart and lungs. These organs drown, so to speak, in the huge stream of blood coming from the periphery during an attack of cardiac asthma. Based on this principle, I have constructed an apparatus called the "Venostat" in order to shunt the blood in the four extremities, and so reduce the engorgement of the heart and lungs. The instrument consists of four blood pressure cuffs in series with a manometer. These are inflated to diastolic pressure and kept at this level for 10 to 15 minutes and gradually deflated. During the compression of the extremities, the blood pools in them because only the veins, not the arteries, are obliterated by the pressure of this degree. This whole subject has been fully dealt with in my paper on dyspnea¹².

Venostasis was applied to this patient and the asthmatic attack stopped in about 5 minutes. This was repeated whenever the attacks recurred. It was not very long before we could keep the patient comfortable with only one application a week.

SUMMARY

The diagnostic triad of syphilitic aortitis consists of angina pectoris, a negative carotid sinus (vagus) reflex, and a rapid blood sedimentation reaction.

The variations and pitfalls of each of the symptoms are individually discussed.

BIBLIOGRAPHY

- ¹BRAUN, L Herz u Psyche, Wien-Deutsche, 1920
- ²DANZER, C S Address before Amer College of Physicians, Boston, Mass, April 11, 1929
- ³CZERMAK, I N Gesammelte Schriften, Leipzig, 1878 I, 779
- ⁴HERING, H E Die Karotissinusreflexe auf Herz u Gefasse, Steinkopff, Leipzig, 1927
- ⁵CHIARI Verhandl d deutschen pathol Gesellsch 1905, IX, 326
- ⁶MONCKEBERG, J G Handb d arztlich Erfahrungen im Weltkriege, 1921, VIII, 11-15
- ⁷JOSLIN, E Annals of Int Med, 1930, IV, 54
- ⁸VOLTKOFF, E Virchows Archiv Pathol Anat u Physiol, 1923, CCLXI, 42
- ⁹WESTERGREN, A Am Rev Tuberc, 1926, XIV, 94-101
- ¹⁰LEWIS, THOMAS The Blood Vessels of the Human Skin and their Responses, Shaw, London, 1927
- ¹¹EPPINGER, H, PAPP, L, and SCHWARTZ Über das Asthma Cardiale, Springer, Berlin, 1924
- ¹²DANZER, C B Annals of Int Med 1928, II, 239

Agranulocytosis: Its Classification*†

Cases and Comments Illustrating the Granulopenic Trend from 8,000 Blood Counts in the South

By STEWART R. ROBERTS, M D , F A C.P., and ROY R. KRACKE, M D ,
Atlanta, Georgia

THIS new disease that we call agranulocytosis is an important addition to the list of dangerous diseases. A biologic condition exists in which the granulocytes are removed from the bone marrow and the blood stream. This is apparently a relatively new condition which emphasizes the necessity for blood examinations, and the fact that the granulocyte is apparently a biologic necessity for life, opens up a whole new world for research upon the blood. In no other condition is there so clearly an opportunity to study possible functions of these cells that have hitherto been unknown. A brief illustration is of value. For four days a strong man fifty-eight years of age feels sluggish and tired, the fifth day has a chill and fever, the sixth day, a higher fever; the seventh day, a slight redness of the throat and a restless stupor, the eighth day, coma and death. There is a negative history of infection, a negative blood culture, only an absence of granulocytes in the blood stream and in the marrow an absence

of granulocytes, myelocytes, and myeloblasts. What is it, and why is it?

Evidence has been presented in a previous paper¹ which showed the cycle of events in this disease. These events develop and follow in an orderly sequence. We have had nothing like it before either in biology or in medicine. In the beginning there is as yet no demonstrable infection, but only a selective hypoplasia or aplasia of the myelocytic cells of the bone marrow. The myelocytic series of cells either completely or nearly completely disappears. About four days after this event, the granulocytes are either absent or nearly absent from the blood stream. About two days after they disappear from the blood stream, the clinical onset begins, often in severe cases with dramatic suddenness, with collapse, chill, fever, red throat or ulceration of the mucosa, and stupor and death unless the granulocytes quickly reappear in the blood stream, because the marrow has begun to make myelocytes. If, and when, sepsis develops, it is a result and complication of the disease rather than a cause.

When the clinician first sees a case sick enough to send for a physician, the patient has usually already gone

*From the Emory University Hospital, Atlanta, Georgia.

†Read at the Baltimore Meeting of the American College of Physicians, March 27, 1931.

through the first three stages of the disease, and death or sepsis or both are at hand. The three stages in order are bone marrow onset, blood stream onset, and clinical onset. The sepsis follows the disappearance of granulocytes from the marrow and blood. And then absence, after two to four days, more or less, causes characteristic mental and physical collapse and a decreased resistance to bacterial flora. Hence the complicating sepsis may result from the variety of bacteria ever present upon the alimentary mucosa and normally prevented from entrance and activity because of the quality of resistance conferred perpetually upon the tissues by the granulocytes. The complete absence of the granulocytes for a period of seven days, more or less, is probably incompatible with life. Immunity in the fullness of its powers is dependent, in large part at least, upon the persistent, daily contributions of these cells. The restoration of myelocytic activity in the bone marrow is apparently the only hope of recovery. Hence those cases that live long enough to develop sepsis have a better chance of recovery. Sepsis, or sterile abscesses, may be therapeutically valuable. Dysfunction of the myelocytic series may recur again and again, causing recurrent attacks of the disease.

As one studies the disease and its intimate problems, its very largeness appears and distinctions begin slowly to separate themselves one from another. The idea of a group of diseases and conditions whose very essence is a decrease in the granulocytes begins to assert itself. This decrease varies from a transient disease, a mild acute

granulopenia to complete disappearance of granulocytes and a tragic blood disease called, among other names, agranulocytosis. It carries with it so far as is known a definite pathology, and certainly a definite series of onsets, that entitles it to be regarded as a disease entity until proof is afforded that it is the result of, or a symptom of, some disease or condition. One studies the books on diseases of the blood and finds in the indices long columns on leucocytosis and but a few scant references to leucopenia, and those chiefly copied from other books and papers. Far more space is devoted to leucocytosis than to leucopenia or to the functions of the leucocytes or to both combined. What indeed is the meaning and what are the ramifications of leucopenia? For example, there are the cases of granulopenia even to the complete absence of granulocytes which result from poisons, septicemias, irradiation, and which characterize some primary and secondary anemias and leukemias and certain acute infectious diseases. And then as one studies several thousand blood counts made under identical conditions of climate, altitude, locality, and identity of race and technique, the impression forcibly asserts itself that the granulocytes collectively are not only mobile, but exceedingly labile as well, far more so than any other blood cell. They enter the blood stream in showers and die in showers, their ups and downs are frequent, the count is up now, the count is down now, but out of all these variations more facts and new groups emerge, revolving around the central fact of a granulopenia. In a large series of blood counts a considerable

minority present a granulopenia, relatively acute in one patient, relatively chronic in another. It is to this phase of granulopenia that we desire to contribute a few facts, tables and conclusions, after a brief consideration of a classification that for the present seems practical.

One very important point to be borne in mind is that the life of the granulocytes in the blood stream is approximately four days, or seventy-two hours, a fact gained by animal experimentation.² The normocyte lives about thirty days. The leucocyte must function very intensely to have so brief an existence and its functions likewise are probably most complex. The functions of the granulocytes are probably more complex and important than hitherto believed. Their important rôle in the ingestion of dead and living bacteria, and their service as a source of important proteolytic ferments has long been recognized. Much evidence has accumulated to indicate that these cells may be the chief source of supply for many of the various types of immune bodies, such as hemolysins, bacteriolysins, precipitins, etc.³ Therefore, when the granulocytes are markedly decreased or when they disappear, the resistance of the patient may fall to a low ebb and easy bacterial invasion may result.

There is evidence that a granulopenia is a more important biologic state and blood condition than it has been considered. An attempt to separate the granulopenias one from another and to classify them may be rather early, in that the classification may have to be revised again and again with new knowledge. Nevertheless it af-

fords us a mental picture of the divisions that make up the group and that constitute the basis for future study.

THE GRANULOPENIAS

1. Acute granulopenia of unknown cause
2. Chronic granulopenia of unknown cause
3. Acute agranulosis with or without resulting sepsis
4. Acute recurring agranulosis with or without resulting sepsis.
5. Chemical granulopenia, due to chemical poisons as benzol and arsenic
6. Septic granulopenia, the result of general or localized septic processes
7. Irradiation granulopenia, the result of exposure to roentgen and radium rays
8. Anemic granulopenia, the condition accompanying certain splenic, aplastic and pernicious anemias, acute aleukemic lymphatic leukemia, lymphatic leukemia and certain secondary anemias with bizarre proportions of the lymphocytes and monocytes
9. Infectious granulopenia, the condition accompanying certain acute diseases as typhoid, typhus, measles, mumps, malaria, influenza, dengue fever and certain pneumonias
10. The granulopenia of Roseola infantum, also called Exanthema subitum

We wish to discuss the first two divisions with cases and comments upon them, after a brief discussion of agranulosis, items 3 and 4.

Acute Agranulosis, With or Without Resulting Sepsis

This is the more common type of the disease. In the cases that die before the onset of sepsis the overwhelming collapse from the mere and continued absence of the granulocytes is so great that death occurs before ulceration, necrosis or septicemia have had time to develop. Only a mild redness of the throat may be present, utterly unable of itself to cause or hasten death. The case given on the first page of this paper illustrates death without sepsis. We consider a case that shows no evidence of sepsis and in whom blood cultures are negative to be non-septic unless at autopsy evidence of sepsis is afforded. One's own experience and the literature more generously, perhaps, afford examples of both varieties. Sepsis is to be regarded as a complication of agranulosis, a result of the loss of the protective immunity afforded by the granulocytes. It will be noted that we propose and have submitted the term "agranulosis" instead of "agranulocytosis." We believe this an improvement in the terminology of this disease, since it indicates the pathological process as clearly and possesses the added virtues of brevity, simplicity, and easy pronunciability.

ACUTE RECURRING AGRANULOSIS WITH OR WITHOUT RESULTING SEPSIS

The remarks just made apply equally well to these cases. There is only one difference, these cases always recover from one or more attacks and have a second or additional attacks. One thinks of the relapse and the remission in pernicious anemia. Every patient with the disease is to be re-

garded as a candidate for a second attack. If he recovers from the first attack, daily blood counts offer the only opportunity so far known to follow the granulocytes upward as they approach normal and downward if the second attack follows and develops. Such counts, if possible, should be made at the same time daily and by the same technician using the same pipette. The granulocytes will show a definite drop to a few granulocytes or to complete absence about four days before the clinical onset begins. This is a better time to begin treatment than after waiting for complete agranulosis. One of our reported cases illustrates the recurring type. The literature affords examples of many recurrences in the same case and at varying intervals. Mild cases may recur at shorter intervals. The second and fatal attack in a man of sixty came ninety days after the first attack. The cause of the recurrence is an interesting problem. In the attack of pernicious anemia, the granulocytes often decrease with the normocytes and the characteristic granulocytes of pernicious anemia seem to be the first blood evidence of the attack and the last after remission has begun. If one could explain agranulosis, he might also be able to explain pernicious anemia.

ACUTE GRANULOPENIA OF UNKNOWN CAUSE

Here we are entering upon a rather chartless sea and much unexplored territory. Three illustrative cases may picture the types.

(a) A man of fifty-one in good health had been under much nervous and mental

strain for two years. At intervals during 1930, he noticed periods of a few days introduced by sleepy feelings, difficulty of waking, slowness and sluggishness of mind and body. After two or three days or a week, he would quickly become well again. A few small lesions of ulcerative stomatitis would occur at this period. On December 1, 1930, an attack came, worse than before, accompanied by heavy lids, sleepy feelings, weakness, a desire to sit and be still or lie and sleep. This attack lasted six days and the white cell count was as follows:

	White Blood Cells	Percent of Granu- locytes	Number of Granu- locytes
December 1	5200	55	2860
2	4500	51	2295
3	4200	48 (ulcers	2016
4	3600	40 of	1440
5	5200	50 mouth)	2600
6	6000	56	3360

For the first five days the patient felt very weak, especially so on the fourth day. He began to feel better on the fifth day though the ulcers were then just beginning to heal. Another attack came on Saturday, March 14, 1931. After a hard week with much loss of sleep and strain, he awoke with heavy, sluggish feelings, burning upper lids, heavy limbs, and through the day, objects were rather dim and distant, memory poor even for events three hours before, and all day a sleepiness. A blood count showed a Hb of 99 percent, W B C 6600 and a differential of N, 46, L, 53, M, 1. The granulocytes numbered 3036, and on the next day, 3428. There were no ulcers with this attack. This patient can now because of his feelings come for a count and describe the onset, and as he says, "feel his leucopenia."

(b) In infants with very red and swollen gums and negative physical examination otherwise, save for temperature of 105°, an acute leucopenia may be the only positive finding.

(c) We have a definite account of a physician who in April, 1927, had an attack of agranulosis with chill, fever, red throat, granulocytes absent, lymphocytes 80. A

second attack came thirty days later. "In the year and a half that followed, whenever I was not feeling well the white count always showed between 4000 and 5000 whites with a corresponding fall in polys. I could always tell when a leucopenia was present. Since my retirement in 1929, I have slowly improved in general health, but it has left me with a myocarditis, and a loss of thirty pounds in weight that I have never recovered."

We have here three varieties of cases. The first in the man is acute granulopenia. In the third case there were apparently similar attacks of acute granulopenia, but he had recovered from two severe attacks of agranulosis. Is acute granulopenia a first step toward agranulosis, a mere difference in degree only, or is it a separate condition? The curious observation of Dr. Hines Roberts⁵ on teething with inflamed and swollen gums, as correlated with the adult with his aphthous ulcers is interesting if not significant.

We have so long looked upon blood counts as the result of extra-hemic states and disease except in the case of primary anemias, and then we have tried hard to find such extra-hemic states, that it is rather difficult to turn the tables and try to find which is cause and which is effect, whether a fall in the granulocytes may be the cause of the subjective body feelings, the weakness and the sluggish inertia of mind and body in these cases. To explain the cause of the fall in the granulocytes is quite another matter. A falling granulocyte count causes symptoms, the greater the fall, other considerations being for the time omitted, the greater the evidence of collapse, provided the element of duration be

also taken into account. The strange disease of infants and children, first described by Zahorsky^a and called *Roseola infantum* and *Exanthem subitum*, pokes its problematic nose into the picture. Here is a disease without symptoms save fever and without signs save an extreme leucopenia of 3000 to 7000, 10 to 25 per cent granulocytes, 75 to 90 per cent lymphocytes, a lymphocytosis, a rash on the fourth day, (a leucocyte lives four days) a fast fading rash on the same day and a quick recovery.

A child of eighteen months was taken suddenly ill with high fever on May 3, 1930. There was a slight gastro-intestinal disturbance. Family history and past history of no importance. Examination negative except a temperature of 104°. The W B C were 3,000, N, 13, L, 86, M, 1. On the fourth day there was the typical rash of *Roseola infantum*. Temperature dropped to normal. Prompt recovery.

And then how much of the weakness in the acute infectious diseases is due to the disease itself and how much to the extreme granulopenia that accompanies it? Under this question might well be included certain cases of dengue fever, influenza without complications and typhoid without complications. Does this extreme leucocytosis in meningitis account for the amazing physical strength and endurance of certain cases as compared with the languor of certain mild influenza or dengue cases? And why is there a leucocytosis in pregnancy with so often the new health, the high spirits and the optimism of the pregnant woman? No matter what causes the leucocyte increase, do more granulocytes, a myeloid rise stimulate strength and energy?

CHRONIC GRANULOPENIA OF UNKNOWN CAUSE

We wish to discuss more fully, item 2 of the classification, namely, a condition which we call Chronic Granulopenia. In 1910, Cabot⁷ called attention to the association of "some forms of debility" with an increased percentage of lymphocytes, "due in fact to the absolute diminution of the neutrophils." Piney,⁸ in 1927, under the title "Leucocytic Pictures" interpreted a difficult case of a mentally defective man with a pain in the right iliac region who at operation showed adhesions around the cecum. The count showed 7,500 leucocytes of which the granulocytes were 48, the lymphocytes 49, and the monocytes 2 per cent. Cabot spoke of the condition as a "false appearance of lymphocytosis." References to similar counts occur in certain cases of the endocrine glands, and Clough⁹ refers to "debility" as one of the causes of the leucopenia. The intimation is rather common that this strange sameness of per cent and number of granulocytes and lymphocytes is the result of the debility, the adhesions, and the endocrine diseases. The lymphocytes are normal in number and size. In such counts the granulocytes and lymphocytes are about the same in per cent and number, so much so that we have referred to such an equality as the "fifty-fifty count," or, if persistent, a chronic granulopenia. If such a count is the result of debility, a neurosis, or, a chronic exhaustion, it is relatively unimportant, but on the contrary, if it may be the cause of such conditions, it becomes of real importance because it intimates that the origin of the syndrome may be in the

bone marrow and the weakness and debility be but a first degree of the real collapse that occurs in agranulosis when all the granulocytes are gone. We have reported a case in a woman who, in 1923, had a count of leucocytes, 7,400, granulocytes, 47, lymphocytes, 52, and monocytes, 1 per cent, or 3478 granulocytes to 3848 lymphocytes. Six years later this woman developed fulminating attacks of agranulosis and died in the second attack. In another case that developed, and died of, agranulosis, the count made was normal two years previously. But it is with these chronic granulopenias that we are primarily concerned and not with their relation to agranulosis. Wellman¹⁰ has recently reported an instance in which the patient complained of marked exhaustion with negative physical findings, but whose blood count was persistently low with a high percentage of lymphocytes. The relation of a few case reports will accent the type and the problems.

Case 1 N B A woman of sixty-one, well nourished, who complained of debility and gastric distress. Her chief complaint was weakness and lack of endurance. There was much mucus in the stomach and in the large bowel. Other examinations proved negative. She was a typical debilitated neurotic, always trying to be better. Her average count was 5000, G, 50, L, 48, M, 2. In one differential count there were 17 "mudge" forms found, 100 cells counted. A sternal puncture showed myeloblasts, and myelocytes as well as young forms of granulocytes in degeneration with vacuoles, pyknotic nuclei, and a few cells beginning to disintegrate.

The contrast between Figure 1, from a case of chronic granulopenia, and Figure 2, from a case of acute agranulosis, is interesting.

Case 2 A M P A man of thirty-nine was first seen in June, 1922, height, six feet, three inches, weight, 140 to 150 pounds. Complaint was exhaustion and lack of endurance. Test meal, total acidity, 50, free HCl 32. Four counts were made from 1922 to 1931, as follows:

	Hb	RBC	WBC	G	L	M
1922	84	4,720,000	5,600	47	53	
1929	73	3,430,000	7,650	51	49	
1930	83	3,200,000	4,800	44	56	
1931	87	4,220,000	5,500	66	32	2

In this case the average of four counts over four years is 5,390 leucocytes, an average granulocyte count of 51 per cent, or an actual number of 2,749 granulocytes. An interesting finding in these patients is the occasional sharp variation in the percentage of granulocytes upward with the corresponding fall of the lymphocytes, and this whether the counts are made daily or from year to year. This is illustrated in the jump of the leucocytes in 1929 which, however, cannot be considered abnormal, and the rise in the granulocytes in 1931. The patient was of the opinion this last year that he was in better health than the years previously, business being so poor that he had been resting much more than usual.

Case 3 W A S A man of forty-eight, minister, weight 141 pounds, height 5 feet, 11 inches, same type physically, though not so tall. Complaint of exhaustion and gastric disturbance. Hypotension. Normal gastric acidity. This man was a research scholar of high intelligence. He "gave out so quickly," he said.

	Hb	WBC	G	L	M
1923	94	5,350	53	43	
1925	78	5,400	65	30	5

In two counts, two years apart, the leucocytes averaged 5,375 with 59 per cent granulocytes or 3,171.

Case 4 C A S A woman of forty-four complained of nervousness, indigestion and easy exhaustion. Weight 110 pounds, height 5 feet, 1 inch. Gastric acidity normal. Both ovaries were removed at twenty-seven. Examination negative. Hb 88, RBC, 5,400,000; WBC 1100; G 48, L 43, M 8. Granulocyte numbered 1,068.

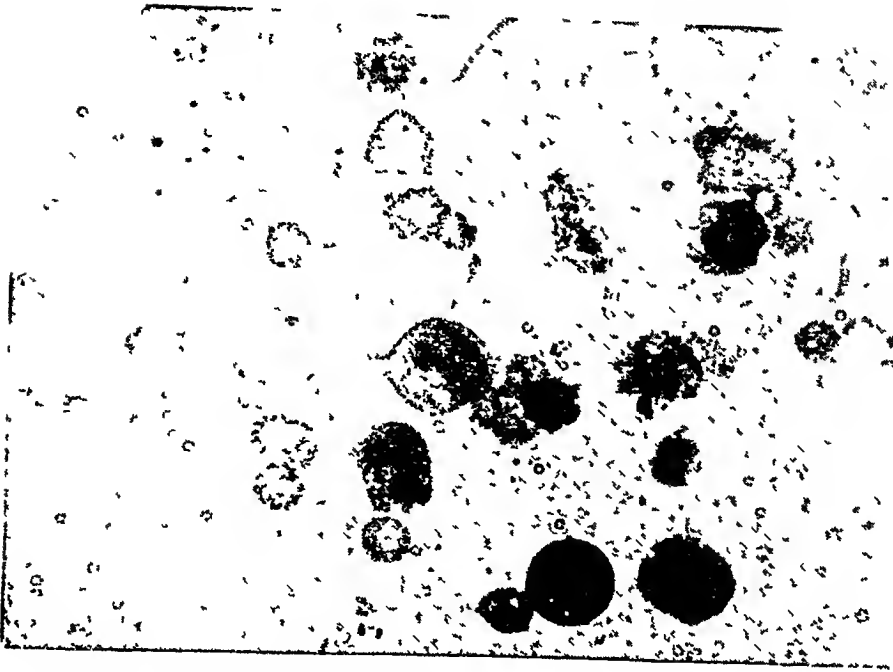


FIG 1 Smear of bone marrow obtained by sternal puncture from a patient with chronic granulopenia. Note the evidence of cell degeneration, including irregularity of contour, vacuolization, loss of staining quality, and smudge-like appearance.

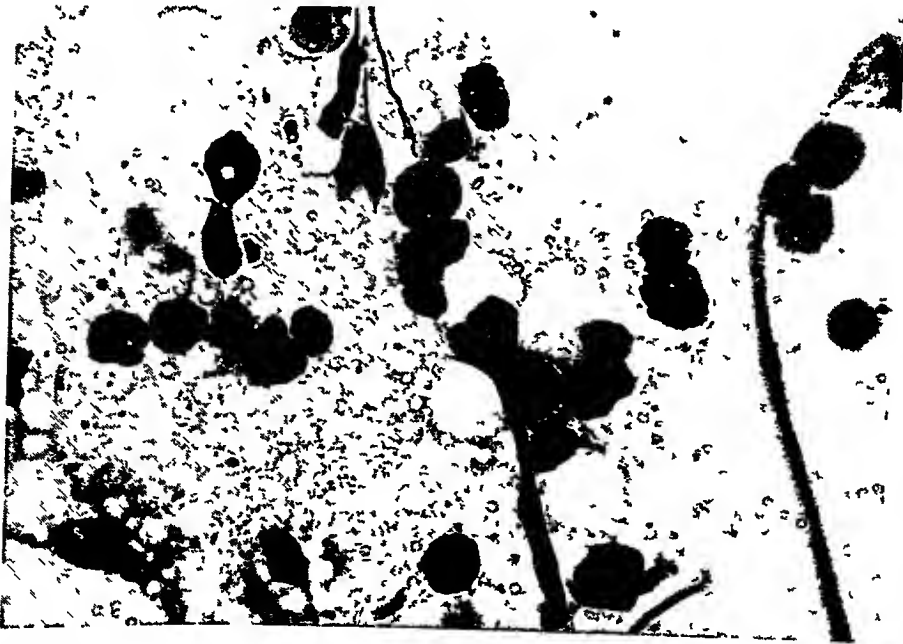


FIG 2 Smear of bone marrow obtained 24 hours before death from patient with acute agranulocytosis without sepsis. Note the absence of granular cells, and evidences of degeneration in those present.

The obtaining of bone marrow by puncture of the sternum has been resorted to in a few cases of agranulosis,¹¹ and there is unanimity of opinion that the essential pathology is a marked and practically complete hypoplasia of the myelocytic tissues. Sternal punctures twenty-four hours before death in one of our patients showed a bone marrow that was entirely devoid of granular cells of any type, including even the myeloblasts.

Such a picture may be contrasted with that seen in bone marrow obtained by sternal puncture from a case of chronic granulopenia. The essential pathology in this condition seems to be unusually severe, rapid degeneration of the granular cells before they have had opportunity to escape into the peripheral circulation. Bone marrow smears in Case 1, (last series, above), show large numbers of so called smudge cells or degenerate leucocytes with numerous poorly staining, irregular, vacuolated, but immature granular cells. Apparently there is either a poor quality of cell produced or an unknown influence is injuring these cells before they leave the bone marrow and before they attain maturity. Special fat stains on these preparations do not show that this is a fatty degeneration.

In an effort to determine whether or not any relationship exists between the degree of granulopenia and certain signs and symptoms, from a large series of patients seen in private practice, a statistical study of 8,000 records was made. The patients comprising this group, for the most part, were those seen in office practice and consultation in the diagnostic clinic of

one of us over the ten year period from 1920 to 1930. Therefore, the class of patients in this group lends itself admirably for such a study, since very few showed acute illnesses in which the hematological findings would be temporarily abnormal. They were ambulatory patients and were not convalescent from any acute infectious disease. The study was conducted with the chief view of ascertaining the number showing varying degrees of granulopenia, comparing the signs, symptoms, and diagnoses of this group with those of the control group, and determining the influence of age and sex in the granulopenic group. The study is presented here in the form of tables and charts, and in certain deductions from the compiled figures, which may be made.

In order to properly classify the 8,000 cases into either the normal or the granulopenic group, an arbitrary standard of normality for the granulocytes was established. Accepting the figure of 6,000 leucocytes per cubic millimeter with 67 per cent neutrophils as being a low standard for normal,^{12 13} all counts below that figure were regarded as showing evidence of granulopenia. Converting this figure into terms of absolute numbers of granulocytes, any count showing less than 4,000 granulocytes per cmm was regarded as being granulopenic. In accordance with figures for normal leucocytes as expressed in various standard text books and by several authorities, we believe that 4,000 granulocytes per cmm represents a low, conservative estimate for normality.

It should also be considered that these white cell counts in this group were usually carried out on ambula-

to 19 patients, in whom the total cell count is probably higher than it would be at bed rest under basal conditions. The importance of this phase of blood counting has been well stressed by Garrey.¹¹ The time the counts were made in this series was usually in the mid-forenoon or mid-afternoon and at a time when the patient was oftentimes on his first visit to the clinic and always at a time when he was undergoing a variable amount of strain and emotional stress coincident with the procedures carried out in a diagnostic examination. From a consideration of the above factors, it is probable that the white cell counts in this series were actually lower under normal conditions than indicated by these records.

From a study of the tables, it will be noted that one out of four patients showed a granulopenia. In the granulopenic group the count ranged from 4,000 down to below 1,000, with a gradual decrease in the number of patients in the more severe degrees of granulopenia.

Total number of records examined	8,000
Number of granulopenias	1,881
Number of normal counts	6,119

COMPARISON OF ACES WITH DEGREE OF GRANULOPENIA

Neutrophile Count	Males	Average Age	Females	Average Age
0-1000	5	47	3	44
1000-1500	13	27	15	39
1500-2000	30	39	59	41
2000-2500	102	40	103	37
2500-3000	126	39	160	41
3000-3500	300	40	335	40
3500-4000	227	45	403	38
Normal Count	2016	39	3274	33

Average of 1000 counts in 1919-20	9022
Average of 1000 counts in 1930-31	8926

GRANULOPENIC GROUP

Counts from 1-1000	8
Counts from 1000-1500	28
Counts from 1500-2000	889
Counts from 2000-2500	205
Counts from 2500-3000	386
Counts from 3000-3500	635
Counts from 3500-4000	630

Since acute agranulosis may be seen chiefly in the patient with granulopenia, this finding seems to be especially significant. In the granulopenic group, ten per cent of the patients came to the clinic with the chief complaint of weakness, in the control group, only five per cent gave this as a chief complaint. This finding seems important since much evidence has accumulated to indicate that weakness, exhaustion, fatigue, and tendency to sleep may be the chief results of a depressed granulocyte count. In the granulopenic group, eighteen per cent gave a chief complaint of nervousness, obscure as the term is, while twelve per cent registered this complaint in the control group.

GRANULOPENIC GROUP

Patients with chief complaint of weakness	190
Patients with chief complaint of exhaustion	75
Patients with chief complaint of nervousness	325
Patients with diagnosis of psychoneurosis	398

NORMAL GROUP

Patients with chief complaint of weakness	330
Patients with chief complaint of exhaustion	246
Patients with chief complaint of nervousness	732
Patients with diagnosis of psychoneurosis	1254

In the granulopenic group, twenty-three per cent of the patients were be-

tween the ages of forty and fifty, in the control group twenty-seven per cent were between thirty and forty. In the granulopenic group, fifty-six per cent were females. Therefore, the type of patients seen most frequently in the granulopenic group, was women between the ages of forty and sixty.

GRANULOPENIC GROUP

Patients in the first decade	46
Patients in the second decade	138
Patients in the third decade	307
Patients in the fourth decade	417
Patients in the fifth decade	434
Patients in the sixth decade	344
Patients in the seventh decade	195
Males	803
Females	1078

NORMAL CONTROL GROUP

Patients in first decade	168
Patients in second decade	440
Patients in third decade	1216
Patients in fourth decade	1661
Patients in fifth decade	1046
Patients in sixth decade	946
Patients in seventh decade	642
Males	2916
Females	3203

COMPARATIVE STUDY OF LEUCOPENIC GROUP AND CONTROL GROUP
AGE

	Leucopenic Group (1881)	Control Group (6119)
Patients in first decade	2.4%	2.2%
Patients in second decade	7.2%	6.0%
Patients in third decade	16.3%	19.4%
Patients in fourth decade	22.0%	26.8%
Patients in fifth decade	22.8%	17.4%
Patients in sixth decade	18.2%	15.4%
Patients in seventh decade	10.3%	10.2%
Males	41%	48%
Females	56%	52%
Average age males	41.1%	39%
Average age females	39.3%	33%

CHIEF COMPLAINT

	Leucopenic Group (1881)	Control Group (6119)
Chief complaint of weakness	10.1%	5.4%
Chief complaint of exhaustion	3.9%	4.0%
Chief complaint of nervousness	17.3%	12.0%
Diagnosis of psychoneurosis	21.1%	20.6%

In an effort to determine whether or not any general differences may be manifest in blood counts done ten years ago and today, an average of 1,000 consecutive counts made in 1920 was found to be 9022, while the average of 1,000 counts made in 1930-31 was 8926. Leucocyte counts, as a whole, therefore, seem to be about the same as ten years ago. Since acute agranulosis has apparently been recognized within that period, this finding may be of some importance.

SUMMARY AND CONCLUSIONS

1. The importance of the leucopenias is emphasized.
2. The biologic and diagnostic importance of a leucopenia is probably as great as of leucocytosis.
3. A classification of the granulopenias is submitted.
4. Two conditions, acute and chronic granulopenia, are described.
5. Agranulosis is classified in the general group of the agranulopenias.
6. The relation of acute and chronic granulopenia to agranulosis is discussed.
7. The problem of granulopenia is studied in 8,000 private clinic patients.
8. One out of every four patients may be expected to have a mild granulopenia.

9 One out of two female patients between the ages of forty and sixty may be expected to show a mild granulopenia

10 The complaints of weakness, exhaustion, or fatigue are twice as frequent in the granulopenic patients as in those with normal white cell counts

11 White cell counts done today show no difference from those done ten years ago

12 A clinical syndrome, consisting mainly of weakness, easy exhaustion, tendency to fatigue, loss of strength and inertia, associated with a diminished number of granulocytes, is described

13 The severity of the symptoms is largely dependent upon the degree of diminuation of the granulocytes, with complete collapse in the most severe type, namely, agranulosis

REFERENCES

- ¹ROBERTS, S R, and KRACKE, R R Agranulocytosis Report of a case J A M A, 95 780 (Sept 13), 1930
- ²WEISKOTTEN, H G The normal span of the neutrophilic leukocyte The action of benzol Amer Jour Path, 32 183 (March), 1930
- ³OPIE, E L Intracellular digestion Physiol Review, 2 552, 1922
- ⁴WELLS, H G Clinical Pathology W B Saunders and Co, 1925, p 200
- ⁵ROBERTS, M HINES Personal communication to the authors
- ⁶ZABORSKY, J Roseola infectilis Pediatrics, 22 60, 1910 Roseola infantum J A M A, 61 1446, 1913 See also Lucas, W P Pediatrics, Macmillan, 1927, pp 833-34 and references pp 840-41
- ⁷CABOT, RICHARD Clinical Examination of Blood Wm Wood and Co, 5th ed, 1909, p 106
- ⁸PINEY, A Recent Advances in Hematology Blakiston's Son and Co, 1930, pp 130-131
- ⁹CLOUGH, PAUL W Diseases of the Blood Harpers, 1929, p 63
- ¹⁰WELLMAN, H E White blood counts Rhode Island Med Jour, 14 51-54, 1931
- ¹¹BUCK, R W Agranulocytosis associated with anal ulcer J A M A, 93 1468-1469, (Nov 9), 1929
- ¹²OSGOOD, E E, and HASKINS, H D Laboratory Diagnosis, Blakiston's Son and Co, 1931, p 170
- ¹³HADEN, R L Clinical Laboratory Methods C V Mosby Co, 1929, p 97
- ¹⁴GARRY, M E, and BUTLER, V Physiologic leukocytosis Amer Jour Phys, 90 355 (Oct), 1929

An Evaluation of the Skin Test in Allergy*†

By H. L. ALEXANDER, M.D., *St. Louis, Mo*

THE word "allergy" as used in these remarks, has to do solely with the clinical condition that is represented by the asthma-hay fever-eczema group of cases. The conception of this type of allergy, as well as its rapid and extensive development during the past fifteen years, has been dependent largely on the skin test. The test consists of the introduction of extracts of foreign substances called "allergens" or "atopens," into the dermal cells. If there be antibodies present to the particular allergen applied to these cells, a reaction in the form of a wheal with a surrounding erythematous zone will appear.

When the test was first developed, it was assumed that an individual whose test was positive to a given allergen was constitutionally sensitive to this foreign substance. By the same process of reasoning, it was inferred that if the nose or bronchi were sensitive, the skin should be sensitive also. This point of view, which is still held by many, has not only been challenged, but from the clinical standpoint, at least has been shown to be fallacious.

*From the Department of Medicine, Washington University, and Barnes Hospital, St. Louis.

†Delivered at the Baltimore Meeting of the American College of Physicians, March 24, 1934.

Allergy is a localized process, and only certain organs of the body manifest it. This holds true, not only for man, but it is seen during anaphylactic shock in animals. The tissues participating in the process have been spoken of as "shock tissues." In humans, most allergic manifestations occur in the skin, in the respiratory tract and in the gastrointestinal tract. Allergy of the heart, thyroid, pancreas, bone, etc. are unknown. Not only do the skin, the respiratory and gastrointestinal tracts bear the brunt of most of the clinical expressions of allergy, but the rule is that but one, or a portion of one, of these systems is involved during a given attack. A patient usually has hay fever, or asthma, or urticaria, or intestinal spasm, and less frequently has two or more of these. In other words, his bronchi alone, for instance, may be clinically sensitive. This is demonstrated by the simple example of the child who has asthma whenever it eats wheat. Wheat, or its digestive derivative, is absorbed into the blood stream and circulates throughout the body. Only asthma results, because in the bronchi alone does the allergen find antibodies with which it will react. The skin may be sensitive, or it may not. If it is, a skin test to wheat should be positive; if not, no positive skin reaction is possible.

With this conception of allergy stated, one may inquire as to the value of the skin test. A difficulty at once arises, because none of the elements that comprise the test have been standardized. There is no one accepted method for preparing allergens, either in their dry state or as extracts. The introduction of allergens into the skin may be done in one of two ways, namely, the scratch method or the intradermal method. The latter is the more sensitive. There is no prescribed amount or strength of allergen introduced into the skin. And finally, the reading of the reactions is entirely an individual matter. This is, perhaps, the most important element, because if the skin be sensitive to a given allergen, some degree of reaction will usually come with any method. On the other hand, a delicate skin, or trauma, will often obscure results. The fact remains, that two observers who use essentially the same technique may report a very great discrepancy in results. One example records the divergence of 25 per cent and 74.9 per cent of positive reactions in bronchial asthma with the same method.

It has been stated that inasmuch as allergy is a localized process, the skin is not always sensitive. There are certain probabilities based on statistics which are familiar to those who deal with allergy. For instance, positive reactions occur more frequently in younger individuals than in adults and tend to disappear toward old age. Positive reactions to foods occur most frequently during the early years of life etc. The reliability of the test however, can be stated only for a given technique performed repeatedly by the

same individual. To arrive at statistics otherwise, requires a consideration of the general results obtained by many observers, each using his particular method. The present study is based on such figures.

TABLE I—POSITIVE SKIN REACTIONS IN 11,443 CASES OF ALLERGY

Allergic Manifestation	No Observers	No Cases	No Positive Reactions	% Positive Reactions
Hay Fever	9	4381	4076	93.2
Vasomotor Rhinitis	8	1020	568	55.7
Eczema (infant and adult)	10	775	408	52.7
Bronchial Asthma	13	4809	2536	52.7
Gastro-Intestinal A1	4	460	122	26.5

These figures coincide with the experience of many who treat large numbers of allergic individuals. There is a prevailing impression that for a reason as yet unexplained, the test is very reliable in hay fever. Here the skin and nasal mucosa appear almost always to be sensitive together. That this has little to do with tissue structure or function is demonstrated by the fact that in allergic rhinitis or "perennial hay fever," wherein the process in the nose is identical with that of annual hay fever, positive skin reactions occur in but 56 per cent of the cases. No sufficient data concerning positive reactions in urticaria and angioneurotic edema could be found but the skin test in these conditions is notoriously unreliable.

Given, then, the average incidence of positive skin reactions in various

manifestations of allergy, the question arises as to whether there are any circumstances which may modify the interpretation of positive reactions. Unfortunately, there are. In the first place these reactions are not always constant. Positive reactions are arbitrarily indicated by + signs. A 1+ indicates a faint response and a 3+ or 4+ a large wheal. With the exception of response to pollens, positive reactions frequently vary in their intensity from time to time. A 2+ reaction may disappear a month later and reappear as 1+, or a negative response in a given case may not remain so, whether or not specific treatment had been given. For that reason, retesting as a routine, is practiced by many. Time will not permit a discussion of the possible factors underlying this phenomenon. Not only may there be variations in positive reactions at different times, but it has been shown that in a given case there may be a wide variation of response if the test is applied simultaneously to various sites of the skin. When these sites are sufficiently varied, a negative reaction may be recorded for the test done on the leg and a 3+ for the one applied to the back (Figure 1). In such instances, it becomes difficult to estimate the degree of an individual's sensitivity by the skin test. The only thing one is permitted to say in that case, is that a certain portion of the skin of the back is sensitive, whereas that of the leg is not.

There is still another consideration of a positive skin reaction which leads to trouble, namely, the appearance of such a response to an allergen which obviously has nothing to do with the

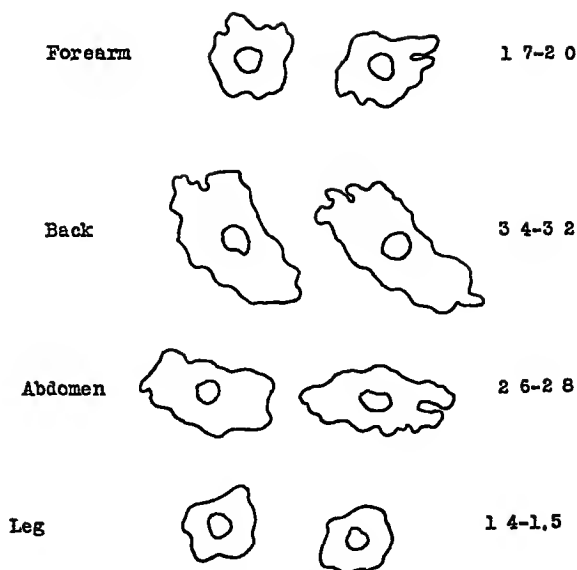


Fig. I

0.02 cc. of a 1-10,000 dilution of ragweed pollen extract injected into various sites of the skin of a hay fever patient

Figures—Area of wheals measured in square centimeters 15 minutes after injection

history of a given case. Such a reaction is termed a "false positive." These occur so frequently that each positive reaction to be considered relevant should be tested clinically. This is done by the withdrawal of the given allergen from the patient's environment with subsequent subsidence of symptoms, and the re-introduction of the allergen with reappearance of symptoms. This, after all, is the only reliable check on positive reactions.

From these data, one may justifiably be discouraged with the skin test, when it is applied to most allergic conditions. This discouragement has been reflected in recent years by many who were led to believe in the adequacy of the test. They have been told that a negative response reflects on their performance of the test, whereas it is not a question of improper technique but of some condition inherent in the patient. (Some specialists use three hundred or more allergens routinely, but their results do not indicate that success lies in mere numbers.) These remarks are not in-

tended to convey the impression that the skin test should be discarded, for it is as yet, by and large, the best means at hand for determining specific sensitivity, and when it works successfully it is most satisfactory.

Allergy is still growing apace and the number of sensitive individuals is, according to statistics, astounding. This fact demands that the great majority of such cases should be treated by the internist rather than by the specialist. An appreciation of the subject is, at best, difficult, and the vast amount of literature concerning it makes things no less confusing. As long as the skin test offered a reliable means of determining the specific allergen responsible for symptoms, there was a fair chance for anyone to work out a case. Since the test appears unreliable and difficult to interpret, some other approach becomes necessary.

One fact which offers a general, workable basis is derived from statistics, namely, that by far the greatest number of patients with allergy, some 80 per cent or more, are sensitive to comparatively few allergens. These, excluding pollens, listed in order, are shown in tables IIA and IIB.

If reliable extracts of these 25 allergens together with a few pollens most common to a given locality be applied to all cases, the chances are that if reactions are to occur at all, they will appear with them. These are the allergens to which one is most exposed. This fact is evident from the high incidence of reactions to such substances as wheat, egg, milk, feathers (pillows), and orris root, (face and talcum powders). Likewise foods that are starred in Table IIB are those

TABLE IIA—INCIDENCE OF REACTIONS WITH COMMON ALLERGENS (32,182 TESTS)

Allergen	No Tests Done	No Positive Reactions	% Positive Reactions
Feathers { * Ch G D	5,491	1,130	20.3
Orris Root	2,537	429	16.9
Horse Dander	2,798	463	16.6
Wool	602	68	11.3
Pyrethrum	1,153	108	9.3
Cat Dander	1,667	154	9.2
Cattle Dander	745	65	8.7
Dog Dander	365	19	8.3
All others less than 5%			
*Ch =chicken, G=goose, D=duck			

TABLE IIB

Allergen	No Tests Done	No Positive Reactions	% Positive Reactions
Wheat	1,999	447	22.4
Egg	923	170	18.4
Milk	1,176	171	14.8
Chocolate	285	40	13.9
*Spinach	330	44	13.3
Bean	822	126	12.9
Potato	604	73	12.1
*Tomato	522	62	11.9
*Carrot	329	39	11.8
*Pea	548	63	11.5
*Barley	644	69	10.7
Rye	946	84	8.9
Pork	508	42	8.3
Beef	527	42	7.7
*Oat	1,711	115	6.7
Corn	1,774	117	5.7
*Rice	635	36	5.7
Pepper	452	79	17.5
All others less than 5%			

*Figures taken mainly from cases of infantile eczema

which are given to infants who, when hypersensitive, are particularly susceptible to food allergens. In dealing with adults, one may omit these particular extracts and thereby lessen the number of allergens to be used routinely

Should no positive reactions be obtained, if the patient be placed in an environment wherein he will not come in contact with these comparatively few allergens, symptoms will disappear in most uncomplicated cases. This is the basic anti-allergic régime in one form or another, on which most specialists place their patients, because these are

the allergens to which sensitivity is most likely to exist. To determine the allergen at fault, the patient is exposed to one or more of the substances suspected until symptoms appear

A skin test correctly interpreted leads to a short cut, and it therefore should be done, at least with the allergens mentioned above. To be sure, there is a residuum of cases sensitive to other substances, or with complications, that require special treatment. A great many patients, however, may be treated successfully if they are protected from some of these common allergens.

BIBLIOGRAPHY

- BLACKFAN, K. D. Am Jour Dis Ch, 11: 441, 1916; Am Jour Med Sc 160: 150, 1920.
- WALKER, I. C. Canad Med. Assn Jour, 9 97, 1919
- SANFORD, A. H. Minnesota Med, 3. 174, 1920
- RAMIREZ, M. A. Arch Dermat. and Syph, 2 356, 1920
- SCHLOSS, O. Am Jour. Dis Ch, 19: 433, 1920
- BAKER, H. M.: Am Jour Dis Ch, 19 120, 1920
- GOTTLIFB, M. J. Jour Am Med Assn, 75: 814, 1920
- CAULFIELD, A. H. W. Jour. Am Med Assn, 76 1071, 1921.
- O'KEEFE, E. S. Bost Med and Surg Jour, 183: 569, 1921, Jour Am Med Assn, 78 483, 1922
- VANDERVELD, A, JR: Am Jour. Med. Sc, 164 97, 1922, 174 101, 1927.
- LATHAM, A, and COKE, F.. Practitioner, 109 121, 1922.
- COOK, R. A.: Jour Immunol, 7: 147, 1922
- GORD, A. G. Jour. Am Med Assn, 80 371. 1923
- CORPER, F. J. Am Jour. Dis Ch, 29 355, 1925
- CHANT, E. H. Canad Med Assn Jour., 15 1240, 1925
- PESHKIN, M. M. Am. Jour Dis Ch, 32 862, 1926
- FINEMAN, A. H. Jour Immunol, 11 465, 1926
- VAUGHAN, W. T. Jour. Lab and Clin Med, 13 24, 1927
- BALYEAT, R. M. Jour. Lab and Clin Med, 13 24, 1927, p 516, Jour. of Allergy, 1 516, 1930
- CLARKE, J. A. Jour. Am. Med Assn, 89 866, 1927
- SMITH, W. A. Mil Surg, 61 560, 1927
- COKE, S. Brit Med. Jour. 1927, 1, 955
- McLAUGHLIN, J. A. Jour Am Med Assn, 89 863, 1927
- ROWF, A. H. Jour Am Med Assn, 91 1623, 1928
- BAAGÖL, K. H. Klin. Wchschr. 7 307, 1928
- RACKEMANN, F. M., and COLMES, A. Jour Allergy, 1: 2, 1929
- EVERMANN, C. H. Jour. Allergy, 1 350, 1930
- Author's Statistics and Personal Communications

The Influence of the Practitioner of Medicine in Guiding the Public Towards Health*

By HAVEN EMERSON, M.D., *New York City*

THE terms of the title assigned to me are too ambiguous to pass without definition. By the practitioner of medicine we usually intend to include only those physicians and their professional associates who earn their living chiefly, if not entirely, by using the sciences and arts of medicine for the diagnosis and treatment of disease as it is expressed in individual patients. Such physicians are by implication distinguished from those who are concerned with the prevention of disease through the authority and resources of official and volunteer health agencies. As I understand the use of words, both groups of physicians and their professional associates, by whom I mean nurses, social workers, dentists, and sanitarians, are practitioners of medicine, the private practitioner, general or special, being concerned chiefly with cellular and personal pathology, the practitioner of public health with social and geographic pathology. Knowledge of prevalence and prevention among the public of such diseases as are believed to be preventable is gradually approaching an exactness comparable to that of the processes and

expression of disease in the individual.

The function of the practitioner of individual medicine is conceived by the laity to be almost wholly the discovery of the nature of, and relieving the symptoms due to disease and defects of all varieties, whether of body or mind; that is to name and to treat disease, to relieve symptoms if possible, to cure sometimes, often to postpone death, and usually to give such comfort and courage in the presence of disease that can with our present knowledge be *neither* cured nor relieved, as the quality of human character permits.

The function of the devotee of public health is, in the words of England's eminent health officer, Sir George Newman, "to make a better tabernacle for the soul of man to inhabit," or in less imaginative terms, to adjust mankind and his environment so successfully that each individual may attain the amplest satisfaction in life of which he is capable, within the limits imposed by his inheritance of qualities and the economic status which society allows him.

Obviously the basic sciences upon which these two closely inter-dependent fraternities of the medical guild have erected the structure and conduct of their work are identical, the techniques and methods of application however

*Delivered before the American College of Physicians, March 24, 1931, Baltimore, Maryland

differing widely As the specialist in personal medicine extends his skill and knowledge far beyond the subject matter of his undergraduate curriculum, he who would deal competently with the group, the communal, the social expression of disease, and seek to accomplish prevention in the mass or the demos must add some understanding of vital statistics, sanitary science, epidemiology and social organization.

When using the term public health we rarely express clearly what is in our minds We are apt to mean merely the sum of individual healths statistically expressed as morbidity or mortality, and their opposites vitality and longevity. To paraphrase an old medical aphorism "There is no health; there are only healthy people."

In no true sense is there such an entity as public health, for the public, the demos, the crowd, the community of whatever size is in a sense perpetual if not immortal and yet lacking personality, and without birth or death can in only a figurative sense be credited with so intimate a quality as health

It is the public as a composite of individuals of all ages and conditions which we wish to guide towards health

May I, in further interpretation of the title, be permitted to sketch briefly the two eras through which we have in a measure passed and suggest the significance of the one at the threshold of which we now stand expectant but confused

From just prior to 1850 until almost exactly 1900 public health established itself in general esteem by the application of sanitary science and the authority of sanitary law to the control of communicable diseases, chiefly those

conveyed by discharges of the intestinal tract, and those transmitted by vermin. The environment was the major issue and by improvement of water supplies and waste disposal, by housing reform and a generally higher level of municipal housekeeping the cities were brought to be a safer place for health than was rural America During this era of sanitation the health officer and his supporting board of health were almost alone in the community in their concern with the application of medical knowledge to the conduct of public affairs. Their functions were chiefly conceived and executed in the spirit of the police, and often mainly for disciplinary purposes Except during the throes of an epidemic, or threat of one they were unheard and unsung, and they lacked support of voice, opinion, or funds from the general public or volunteer associations.

With the initiation of the educational and social effort of the local committees for prevention of tuberculosis in 1900 and the following years, and the subsequent creation of the National Tuberculosis Association, there came a new, powerful and effective element which has stamped its character upon every phase of public health work here and abroad for the past thirty years We may speak of this second era as that of public instruction It was the statesmanship of Prudden, Janeway, and Biggs in New York and of their counterparts in other eastern seaboard cities which determined the features of this innovation in public approach to the then dominant cause of death. With the simple trio of facts in mind that tuberculosis is communicable, pre-

ventable, and curable it was clear that until every household in the land knew their significance, and could be persuaded into action, no amount of sanitary law or authority, no regulations or restrictions could be expected to avail.

It would be quite superfluous in addressing a medical audience today to elaborate upon the developments in the various special fields of health endeavor which have at times threatened to submerge science and reason in a welter of unrestrained propaganda and publicity. Enough to remind you of the essential similarity of plan by which social hygiene, child health, mental hygiene, heart disease, cancer, blindness, etc., have been brought to public notice in the successive waves of zealous health promotion.

It is true that state laws have in some places required the inclusion of simple facts about the causes and means of prevention of the common communicable diseases, Michigan leading far in the van. But it will be admitted I believe that it has been through the instrument of volunteer and chiefly lay organizations that the people, the public press, legislators and public officers have been reached with the message and promise of preventive medicine. If other evidence were lacking it would suffice to recall that the first division or bureau of a city health department entrusted with health education dates from 1914, and that the first such division of a state department of health was created in the following year.

You know, I am sure, the significant accomplishment of this second era, the stage of widespread public information about health and its attainment, dis-

ease and how to avoid it. Authority of statute law or local ordinance could not assume to require people to seek medical opinion for symptoms or signs of disease which in the private opinions of 1900 did not justify personal anxiety, prevent present enjoyment of life, seem to threaten self support or actually communicate disease to others. And yet prevention depended upon preparedness and priority. Every lesson of the laboratory and clinic taught us that a wide range of the less acute preventable diseases and postponable causes of death could be controlled or reduced only if the patient's discomfort was displaced by a physician's pre-science as indicator for precautionary treatment or adjustment in the way of life.

The clinic of special skill for early recognition of disease, for its consecutive and persistent treatment, including guidance socially, economically, educationally, and often vocationally, was the professional resource towards which public health information was designed to persuade people.

We are still accruing incalculable benefits from the era of sanitation. We have hardly abated a jot in our devotion to the methods and objectives of the era of public information.

And yet we are fairly launched upon a most promising third phase, the era of general personal participation in health, and it is to a further definition of this, and with the hope of convincing you of the desirable function of the general practitioner in advancing it now and in the immediate future, that I wish to devote the main argument.

The date of origin of this era can

be quite precisely given as the Spring of 1922 when both the National Health Council, and the American Medical Association declared themselves of the belief that further advance in the application of preventive medicine demanded the widespread practise of the periodic health examination as a part of the service of the family practitioner of medicine.

This was not even nine years ago a new idea, for experience with a wide variety of public clinics, created under health authorities, in schools of medicine, in hospitals, and under social and philanthropic agencies had brought to accounting and attention an undreamed of mass of submerged and neglected invalidism, in persons carrying on their work and avocations without thought of complaint or belief that there was any other lot for them than handicapped existence.

Out of every ten persons coming for expert opinion on a possible or suspected pulmonary tuberculosis, seven are found to be non-tuberculous, and yet bearing a burden often of another remediable or at some stage preventable condition. In every hundred children presenting themselves for schooling at least 65 per cent are found to have one or more potentially if not at the time, disabling and preventable defects. Every review of bodily fitness among men and women whether for industrial or military needs, or for civil employment, reveals the extent to which unnecessary and readily avoidable disease or disorder of function and structure can prevail without knocking at the attention of the patients or driving them to seek medical care.

What is proposed in order to put to

work the knowledge of prevalence and prevention of disease, which has been accumulated with care and precision in hundreds of educational and research institutions, and by the contributed devotion to fact of still more thousands of medical practitioners? What is the influence which physicians in their personal relationship hold which is of greater persuasiveness towards health than can ever be the authority of law, its enforcement by public officials or the ingenuity and plausibility of generalized popular health promotion through slogans, campaigns, drives and objectives of volunteer or non-official health agencies?

The influence, potential and actual, of the practitioner of medicine, though small in amount at present and applied but haltingly and with diffidence, in persuading the public towards health is seen at its best in pediatrics and obstetrics. It consists in his knowledge of healthy structure and function, deviations from which he has in the past been chiefly concerned with detecting, measuring, and treating. Physiology rather than pathology is the basis upon which his power of direction of human life in health is built.

The obstetrician whether in the person of the specialist or of the general practitioner has accepted evidence accumulated by studies of a statistical and epidemiological character to the effect that prenatal supervision of the expectant mother can be relied upon to reduce the proportion of stillbirths, lower the neo-natal mortality rate, i.e., deaths in the first month of life, and increase the probability of survival of the mother with a minimum of post partum morbidity. Incidentally good

prenatal care at present carried out contributes largely to a reduced prevalence of syphilis. In his capacity of private practitioner of medicine the physician called upon to guide the pregnant woman can and does contribute to the sum total of community health to a degree and in a quality of service which it is most unlikely any other professional agency can replace.

Health departments may for the *dependant* expectant mother facilitate by organization the provision of medical and nursing care during pregnancy, and at and after confinement, but it will always remain for the private practitioner to exert the greatest influence in this field.

At the present time probably not as many as one quarter of the expectant mothers of this country are receiving a medical guidance towards health which is known to be desirable, economically practicable, and productive of a very tangible degree of life saving.

It remains primarily for the physician in private practice to persuade his families of the value of prenatal supervision.

It is to the pediatricist, however, that public health owes its largest debt of gratitude, for it has been to his credit that the healthy babe put in his trust at birth has received increasingly complete health service, whatever the economic status of the parents, until the child is by law at liberty to engage in self-support and escape the application of compulsory education.

No single element in the advance of preventive medicine has contributed so much to the increase in average expectancy of life, to the prevention of

infant mortality, and the reduction of many of the communicable and nutritional diseases of childhood, as has the introduction of health supervision, as a function of the ordinary personal or family practice of medicine, and into the routine of organized public health work.

In infancy, during the pre-school age, and for school children it is now usual to provide, at public expense where necessary, but to an increasing degree through the family physician or the child specialist, a supervision of growth and development, the establishment of at least two specific active immunizations, and medical and dental health examinations, at appropriate intervals, not for the purpose of detecting disease but with the object of establishing and maintaining life, and its most important functions in childhood, growth in physiological equilibrium, together with avoidance so far as may be of communicable diseases, and developmental defects. We know now that where our city communities are alert to use and supply health services for children, of those from two to five years of age 75 per cent or more have at least an annual medical examination, 30 per cent have a dental examination, 35 per cent to 50 per cent are vaccinated against smallpox and about 50 per cent are known to be immune to diphtheria. In no community are these four measures compulsory for pre-school children and it is to be hoped they never will be. In but few are any but smallpox vaccinations required for children entering school. The influence of the medical practitioner and his associates is seen at its best in that field of preventive medicine where

there will probably never enter the authority or obligation of law or ordinance. No advocacy of health measures is listened to with the respect accorded to the family physician's voice.

Each specialty of medicine and surgery has awaiting it a field of effort similar to that so vigorously cultivated by the obstetrician and the pediatrician. The orthopedist, ophthalmologist and neurologist share with the dentist, the internist and the dermatologist a responsibility for guiding the public towards health by appropriate personal persuasion and example.

The success of each organized effort for control or prevention, whether directed against tuberculosis, syphilis, cancer, diabetes, emotional catastrophe or blindness, has been created in the relationship between physician and patient in which the former matches his skill, his imagination, his physiological acumen against the probability or significance of sub-clinical manifestations of disease, or his knowledge of the usual results of disorderly or immoderate ways of living.

The individual physician can rarely accumulate sufficient personal experience with disease, or the variable conditions under which health occurs, to avoid a high degree of probable error in his conclusions as to the relation between cause and effect of personal habits, over weight, under exercising, short sleeping, too much, or disproportional eating and drinking. He needs must rely up on massed experience, and learn to apply other people's assembled facts to the individual man or woman before him. He must learn that there are at least as many ways of healthy

living as there are kinds of disease, and that the essence of his particular privilege is attaining the optimum of health, not the mediocrity of average health, or the mere negative success of freedom from disease, for the client who seeks his guidance.

We have attempted through government great accomplishments in mass prevention of disease. There are now incorporated into our social order functions which could under no safe conditions be trusted to the individual or to the family. We pay perhaps a half dollar, at most a dollar and a quarter, often not more than 25 cents apiece each year to secure the administration of public service for health. Of this about a cent and a half a year goes for the registration and analysis of births and deaths, 8 cents for communicable disease control other than hospital care, 4 cents for tuberculosis, and a cent and a half for venereal disease control, the price of half a glass of milk, 3 cents, to guarantee a tubercle free pasteurized milk supply, as much as five cents apiece for the safety of maternity and infancy, thirteen cents for school health, a trifle of ten cents for food and environmental sanitation, four cents for laboratory work, with six cents for administration including health education. And all this is for a rather crude broadcast type of mass protection. And yet how priceless the benefits, how totally has the outlook of man and his wife and child been altered by even this wholesaling of health. In Philadelphia in 1929 the per capita cost of medical care of all kinds was \$52 of which about two dollars went for prevention. The people of an average midwest rural county

spend \$22 per capita each year, of which about 2 per cent is for health. The health officer must operate his specified services under the limitations imposed by partisan politics and insecure tenure of office, by restricted funds, by the tardily advancing common sense of the populace, and he sees much ahead which he can do to improve water, milk, public understanding, immunity, and physical environment, but even the ablest and best supported, the honest and fairly permanent commissioner of health of state, county or city will quite frankly declare, or admit if challenged, that his potentiality for good is but a fraction of what can be the certain result if physicians in private practice were to enter with as much determination upon health guidance, as they now devote to disease detection and repair.

The future of preventive medicine, the adding of the next and most difficult ten years to the expectancy of life, awaits the universal participation of the practitioner of personal medicine and his patients in the practical use of our abundant knowledge of health development and protection.

It will not be by compulsion or ordinance that the obese, arteriosclerotic, diabetic, or cancer patient will begin to decrease among us, or survive into the allotted seventies, but by such universal voluntary self-interest in health and the management of the later decades of life as will permit the detection of pre-clinical signs and symptoms which may lead to prevention by minimal changes in the conduct of life, without the panic fear of late inevitable disclosure of advanced irremediable disease. Only through the words of the family physi-

cian trusted in birth, sickness, and death will parents and other men and women be persuaded to legitimate and persistent interest in health, and this only when the example of the physician toward his own family and dependents carries conviction of his sincere belief that personal medical practice is capable as much of advancing individual health as it is of relieving and sometimes curing disease.

The influence of the practitioner of medicine in guiding the public towards health is as yet unevenly applied, doubting, almost scoffing, except for the beginning periods of life and growth. It is capable of benefits, to a degree so far surpassing the possibilities of public health agencies, as to justify criticism that it is too timidly conceived.

Constructive nurture often assumed under modern medical statesmanship to be the province of public health becomes effective only when it has lost the implication of generalities and assumes the character of personal guidance by the practising biologist of today's society, the family physician. To quote from a recent article by Lord Dawson of Penn, "The more the cost of social policy is centralized, the farther its administration removed from the man who receives the benefit, the more apt is that man to lean upon a prop, to become a creature of fate rather than a master of effort." The influence of the family physician is at its best when it activates the individual to acquire health by the exercise of his own character, to prove to himself that health is a by-product of initiative and effort.

We have adapted ourselves more ef-

fectively to our zoological enemies than to the successes of our material prosperity and the mechanization of today's existence

Are we not committed by our professional philosophy to that third gospel as Dr Osler described it. "The gospel of his body which brings man into relation with nature, a true *evangelion*, the glad tidings of a conquest beside which all others sink into insignificance, the final conquest of nature, out of which has come man's redemption of man"? Whether we dream with Plato or fling out the challenge with Dr. Holmes—the temper of thought remains the same. Plato looked to the day "when our youth will dwell in a land of health and fair sights and sounds, and receive the good in everything, and beauty, the effluence of fair works shall flow into the eye and ear like a health giving breeze from a purer region and insensibly draw the soul from earliest years into likeness and sympathy with the beauty of reason"

Dr Holmes, in addressing the predecessor of our present public health association in 1860, foretold the chang-

ing emphasis from curative to preventive medical practice, and gave prophesy to the thoughts of today in the following stanzas

"What though our tempered poisons
save

Some wrecks of life from aches and
ails:

Those grand specifics Nature gave
Were never poised by weights or
scales!

God lent his creatures light and air,
And waters open to the skies;
Man locks him in a stifling lair
And wonders why his brother dies!

In vain our pitying tears are shed,
In vain we rear the sheltering pile
Where Art weeds out from bed to bed
The plagues we planted by the mile!

Be that the glory of the past;
With these our sacred toils begin:
So flies in tatters from its mast
The yellow flag of sloth and sin,

And lo! the starry folds reveal
The blazoned truth we hold so dear
To guard is better than to heal,
The shield is nobler than the spear!"

The General Practitioner and the Public Health Program*

By FELIX J UNDERWOOD, M D, F A C P, *Jackson, Mississippi;*
President, Southern Medical Association

IT IS to the credit of our profession that its members have interested themselves actively in good government, and especially in those functions that have to do with the physical well-being of man and that involve applications of medical art and science both in the prevention and the cure of the diseases which afflict mankind

There is not a single point at which public health and private medicine cannot march forward in peace and good will. Our profession is traditionally committed to the prevention, as well as the cure, of disease. Out of its early labors arose the first slender shoot of this magnificent tree of health that is beginning to bear good fruit today. From its membership have come our foremost public health leaders. Be it said to the everlasting credit and to the honor of American physicians that they are watering, fertilizing, and protecting this tree of life in the midst of the garden of our united effort against the insects and poison bugs of ignorance, superstition, and of rampant quackery which establishes so-called health institutes, health homes, adver-

tises so much about your health and often puts it over on a gullible uninformed public and yet knows little or nothing of medicine, either curative or preventive, notwithstanding the fact that they pose as physicians and talk glibly and advertise freely to prevent and cure all diseases which afflict the race. They bitterly oppose the principles and practice of preventive medicine, denouncing immunization and vaccination. They profess not to believe in the germ theory of disease yet so ignorantly inconsistent are they that most of them now tell people that immunization and vaccination cause many diseases such as syphilis, typhoid fever, meningitis, and within this week I have had otherwise intelligent people call me and tell me what "doctor quack" said about it.

Do we need a consistent, persistent program of health education and demonstration backed up by the physician one hundred per cent for the enlightenment and for the protection of our citizenship in every county, in every community, in every home, and with every individual in our State? Do we? Health education like Christian education is a real job in this day and time when evil forces are presenting

*Delivered at the Baltimore Meeting of the American College of Physicians, March 24, 1931

a united front We must stand united in our efforts or we fail miserably.

The most obscure physician gives some portion of his energies to the conservation of health and usually lends his voice in support of public health measures.

Lack of information is a universal fomenter of strife For the physician disciplined in diagnosis and therapeutics, the private relationship between patients and practitioner circumscribes his horizon. That medicine also fills a public relationship, in which the good of the individual may frequently be submerged by the greater welfare of the group, is outside the compass of his vision. He is unwilling to admit that a mass of information and a technique have grown up within the realm of preventive medicine and sanitation that are generally ignored in our medical schools, yet are just as valid as the subjects regularly taught The smattering of so-called "hygiene and public health" that was forced on him in student days appears to him to comprise all that is or needs to be known Every health officer is acquainted with private practitioners who freely admit their ability to fill any public health position with distinction with no previous training. A mind that is permanently closed to new knowledge in other spheres than its own will discount all such new ideas as negligible or subversive of the regular order. Even the physician with a reasonably flexible mental apparatus is often amazingly uninformed of the first principles in preventive medicine and sanitation, a field so closely allied to his own that curiosity alone would seem to compel superficial acquaintance Out

of this lack of information grows resentment toward even the simpler routine procedures of common sanitary practice. An attitude is created which evinces itself in unthinking resistance to all that bears the label of public health Fortunately, this inertia is not often found among physicians

However, not all of the blame is on one side. The public health worker must share some of it, for he fails many times to make any effort to enlighten the physicians within his field as to his plan and methods A full explanation, at the outset, would usually convert medical opposition into acquiescence, at least, if not hearty support His first duty is to educate the doctor, for we are all laymen outside our own specialties In this, as in every succeeding step of his program, the utmost tact is essential Painful memories rise to haunt the health executive who has had under his direction any number of workers. He has seen, more than once, an initially friendly group of medical men turned into enemies of the entire health program through rudeness, arrogance, superciliousness, bad temper, or lack of public health training on the part of a new worker The medical profession has suffered much at the hands of such as these Unsound judgment in selecting a project, or offensive methods of promoting it, will also alienate friends

Of one cause of medical opposition, selfish, mercenary motive, the less said the better. But all experienced health officers have felt its force. The physician of this caliber is so frequently aggressive and "successful" that he holds an influential position in his com-

munity By underground methods he can defeat an honest, well considered project without revealing his hand That he fears the specter of diminished business is simply evidence that his selfishness is matched by his ignorance, for the real all-time well trained health officer is a press agent of scientific medicine Or this kind of physician may covet a place on the public payroll for the money or the publicity to be had out of it In any case his personal gain is made to transcend the public welfare

We who hold positions with the government are always under some suspicion—a suspicion that seems to be growing stronger of late, that is taking the form of a great fear, fear of ultimate domination over all life by an autocracy of bureaucrats Perhaps some of this suspicion is deserved Dictatorial, grasping, impractical, politically partisan persons are found in health departments as in other branches of the government To inject a degree of humanness into an office crowded with necessary routine, to retain a sensitive awareness of the multifarious viewpoints in a large constituency, is no sinecure Yet the more successfully it is done, the more fully will needless suspicion of governmental agencies be overcome It is a paramount duty of all public health executives

Granting, then, that there is sometimes divergence of interests between public and private medicine, where there should be convergence, that there is antagonism where there should be accord, it will be profitable to consider its effects They will manifest themselves in two directions retardation

of sanitary progress in many quarters, and a growing distrust of the medical profession on the part of the public Enough examples have been given earlier to clarify the first point, that lack of medical support, or active opposition, will delay legitimate public health developments But the effect of this attitude on the lay mind may not be so evident to the private practitioner To the medical health officer, standing midway between him and the public, a view in both directions is possible He catches a sense of frustration and of growing exasperation among the laity, that is not revealed to the family doctor so freely He finds the public demanding more service, while his medical colleagues criticize what is already given He realizes that the public is often more fully "sold" on the health program than is the profession His dilemma is sometimes acute As a public servant, his duty is to do the public's will Yet, if he accedes, it will bring to light the reactionary tendency of the medical group He feels himself a Judas among his brethren If such a crisis arises, as it has repeatedly, the layman develops a distrust of the physicians, he is openly critical of their motives and his resentment is likely to be extreme Are not the proposals for health insurance partly the result of just such a process? Are they not the grasping of the public after some method whereby the benefits of curative and preventive medicine may be made available to all, and at once, without waiting for the medical profession to arrive at a broader social outlook? This is not the sort of thing that the great body of health workers

desires, but it is a very natural reaction of enlightened public opinion. "Phantom" this public opinion may sometimes be, but it is a ghost that takes on substance as it gains momentum.

If the discussion so far is a correct interpretation of trends, some solution is sorely needed. Not that we may hope to change human nature, if the fault lies there, but that we may try to bring about more intelligent understanding on both sides and a resultant solidarity now lacking.

Beginning with his earliest medical training, the student should be made to see how his subjects are related to public health. In bacteriology he can learn the uses and duties of state and city laboratories, the methods pursued by them and interpretation of their reports. Lecturers on practice of medicine ought to lay more stress on sources and modes of infection, on ordinary control measures and on the duty of the private physician to protect the community as well as his patient. Courses in pediatrics open the way to the whole field of child hygiene, while obstetrics holds the same relationship to prenatal and maternal hygiene. Medical jurisprudence embraces legal aspects of the practitioner's public health functions. And, lastly, the course in preventive medicine, hygiene, and sanitation should be the point at which these strands are woven together; where the embryonic doctor sees the whole public health field, and comprehends the fact that he has a prominent and inescapable position in it. Do we have such correlation in our medical curriculum today? Hardly. Most of the men who are teaching major sub-

jects in the schools are themselves lacking in this vision. Can more be expected of the people, when their leaders fail?

The medical practitioner has a real place in the public health field. As a matter of fact, preventive medicine is going to consume an even greater proportion of his time. This does not mean those ordinary things that are expected of every conscientious doctor, such as early reporting of morbidity and of births, administration of prophylactic biologic preparations, efforts to protect the community against the infection of his patient, and occasional help in various clinics for the indigent. These he does now to a greater or less degree. But preventive medicine has taken on a broader meaning in recent years. There has come a realization that humanity can be made healthier, and happier, by the early detection and correction of minor deviations from normal, than by curative measures applied after these conditions have produced gross pathology. "Positive health" is as good a name as any for this new objective. And the family doctor is its prophet. Better than anyone else, he can, if he will, make the next generation more fit than its predecessor. This calls for a personal relationship that no governmental agency can so satisfactorily provide. Opportunity is in the making for the private practitioner to take his own peculiar place in the public health movement. Technical preparation there must be, exactly as one would fit himself for any other special procedure. A new approach, a new viewpoint, must be acquired. He is dealing with a well man who wants to keep well.

The health officer prepares the way by education and the physician should make ready for the future that lies in that direction. The American Medical Association has repeatedly endorsed this program. Likewise, state and county societies here and there have caught the meaning of it. But until the man in general practice makes it a real part of his everyday business, it will remain only a pleasant topic of conversation. This is the challenge of the sanitarian to the private practitioner.

Wrapped up with these matters that have been touched on are problems of the medical profession far more profound and significant. What does it mean that there is an active demand in some quarters for a kind of state medicine? Why do we see such contemptuous disregard for the fine fruit of scientific medicine, while any new and blatant cult receives enthusiastic welcome? Opposed as these two trends may seem on the surface, they arise from a common source: lack of socially minded leadership within the

profession. Broadminded, strong, resourceful leaders can point the way and can knit our individualistic membership into a well coordinated group for the solution of these difficulties. Without that, we may have forced on us a ready-made scheme of social medicine.

In other words, the public wants and demands a complete program of health and healing, of which every individual may have the benefit without undue sacrifice, and it is going to have its way somehow. We have the requisite knowledge and skill. Are we intelligent enough to cooperate in meeting this need with a plan of our own devising?

This may seem far removed from the subject of "The Relationship of the Private Practitioner to the Public Health Program," but it is not. That relationship is merely an expression of his outlook on life. The keener our sensitiveness to human need in the aggregate, the brighter will be the hope of fulfilling our ultimate destiny as a profession.

Editorials

EDITORIAL POLICIES

That there will be no abrupt change in those editorial policies under which the *ANNALS* has prospered so greatly, it is needless to state. The present editor has been in close touch with the development of this journal during the past seven years and is fully in accord with the general plan of its organization and production as it has been evolved during that period. He will constantly strive to make the *ANNALS* representative in the highest sense of the American College of Physicians of which it is the official organ. He believes that this can best be done by continued emphasis upon the quality of its scientific articles in order that they may represent, in so far as is possible, not only the most advanced but also the most mature, medical opinion of the times. To this end he invites the submission of manuscripts from both non-members and members of the College and promises that careful consideration will be given to all. Since there are certain fixed limitations upon the size of the annual volume, selection of the most useful material must be made and authors whose manuscripts are returned to them are urged to bear in mind that there are other considerations than the actual worth of the subject matter of a communication which may lead to its rejection. It may deal with a field which is not of

interest to a large number of the readers of the journal; it may treat a subject in too extended a manner to be suited to the size and spirit of the *ANNALS*; the same subject may have been discussed in a recent number, or another paper covering the same ground may have been accepted but not yet published.

In general, the freedom in respect to diction and style which has been allowed authors in the past will be continued. No effort will be made to develop uniformity of expression at the cost of individuality. The editorial pencil will seldom be used except to correct verbosity and ambiguity. However, in the interests of better appearance, greater economy in production and heightened usefulness, the bibliographic references are to be standardized within certain limits. Brief directions in regard to the form desired may be found on the back cover of each number.

In order more fully to represent the broad interests of the American College of Physicians it is hoped to place upon the editorial pages rather frequently communications from those whose special interests, training or experience give their opinions authoritative weight. Such contributed editorials will be initialed to differentiate them from those for which the editor is alone responsible.

CARBON MONOXIDE DEATHS

Litigation based upon the circumstances attending carbon monoxide, and particularly 'garage', deaths is constantly increasing. Physicians should exercise great care in certifying to the cause of death in such cases. The question which usually arises is as to whether death was accidental or suicidal. Since investigation of possible motives, of the behavior of the deceased in the last few hours or days of his life and of all of the minute details of the surroundings amid which the body was found may be necessary for reaching a decision, it is evident that the physician who answers an emergency call and determines that death has occurred cannot be expected to pass final judgment upon the question of accident or suicide at the moment. Unless he is himself a coroner or coroner's physician it should not be his duty to do so at any time, but the family of the deceased may look to him for an opinion. There have been numerous instances in the last few years which make it evident that knowledge of 'garage' deaths is so generally disseminated among intelligent laymen that not infrequently the stage is elaborately set to conceal the fact of suicide. This is especially apt to be true when a man carrying heavy accident insurance, or recently insured under a policy with a suicide clause, and in serious financial straits, plans to take his own life in such a manner as to improve the financial position of his family. Tools may be scattered about, oil or grease applied to hands

or clothing, the hood of the car raised, and the body found in a position consistent with repair work or adjustment of some part of the motor.

Another difficulty which has arisen attaches to the use of the word 'poisoning' in connection with carbon monoxide deaths. The phrase 'carbon monoxide poisoning' has become fixed in medical parlance, but in a recent instance a Circuit Court Judge dismissed a case in which it was sought to secure compensation for a carbon monoxide death under an accident insurance policy in which there was a clause setting forth that no liability existed for death from poisoning. The deceased was found dead in his garage and the question of suicide was not raised by either party to the issue. Certainly the non-medical use of the term 'poisoning' in such a policy, and in all probability the understanding of it by both the vendor and purchaser, should not have been such as to exclude accidental death from inhalation of carbon monoxide from compensation. If such rulings stand unchallenged they will prevent compensation for a large group of undoubted accidents in which toxic agents are instrumental in producing injury and death. In the instance in question the trial judge was entirely satisfied by the fact that death had been certified to as due to carbon monoxide poisoning. Physicians may be forced to adopt some such circumlocution as 'death from inhalation of carbon monoxide', and the phrase *asphyxia carbonica* is justified by long usage.

SPONTANEOUS RUPTURE OF THE SPLEEN IN INOCULA- TION MALARIA

While traumatic rupture of the spleen from falling from a height and from contusion and compression of the abdomen is relatively common, spontaneous rupture has always been a rare condition. It has been known to occur in typhoid fever, typhus, recurrent fever and occasionally in accidentally acquired malaria. All of these conditions have in common the possibility of a rapidly developing splenic tumor through congestion and lymphoid hyperplasia. In ordinary malaria, however, spontaneous rupture of the spleen is a very rare complication. It is said to have occurred but three times in 30,000 cases of malaria observed during the building of the Panama Canal. A number of authors leave the impression that in inoculation malaria for the treatment of paresis a splenic tumor seldom develops, but that splenic enlargement can occur and may be so marked as to produce spontaneous rupture has been shown by several cases. Jutz and Jacobi (*Munch med Wchnschr*, 1931, lxxviii, 395-396) describe an example of this accident which they claim to be but the third to be reported as occurring in the course of the treatment of paresis in which there was no question of the spontaneous nature of the rupture. Their patient was a tabo-parietic, thirty-nine years old who had been inoculated with malarial blood twenty-three days before. He had reached his seventh cycle of a typical malaria, each with a fever of 104 degrees or above, when he suddenly went into a state of collapse with coma, pallor, rapid shallow

breathing and a feeble pulse which soon became imperceptible, death following within a few minutes. There had been no possibility of trauma. At autopsy a hemoperitoneum of two liters was found. Hemorrhage had occurred from a rupture of the greatly enlarged spleen, the tear reaching from the lower pole nearly to the hilus. After bleeding out, the spleen still weighed 540 grams. An entirely similar case came to autopsy in the Department of Pathology of the University of Michigan several years ago. This patient, under malaria treatment for tabo-paresis, had successfully completed thirteen chills during which the temperature ranged between 100 and 104 degrees. Following his fourteenth paroxysm he suddenly became dyspneic, vomited profusely and his pulse rose to 150, death following almost immediately. At autopsy the peritoneal cavity was found to contain over two liters of fluid blood and blood clot. The spleen weighed 580 grams and its upper pole was covered by a large mass of blood clot beneath which there was a rupture of the capsule and eversion of the soft pulp. When the rather limited application of malaria therapy is considered, it seems not unlikely that rupture of the spleen is more apt to occur in this group than in those having naturally acquired malaria. The reasons for this can only be surmised. It would be important to learn if those dying from rupture of the spleen in acquired malaria show a higher incidence of syphilis than the entire group from which they come. Can rupture of the malarial spleen in the syphilitic be attributed to changes in the supporting stroma, a loss of elasticity perhaps,

as part of that 'Derbheit' which gross pathologists recognized more than a generation ago? Or is the cause to be sought in cardio-vascular changes, due to which the splenic congestion of malaria is imposed upon a preceding con-

gestion of luetic origin? At any rate, the occasional occurrence of this accident is an added argument for investigating the efficacy in the treatment of progressive paralysis of other agents capable of inducing hyperpyrexia

Abstracts

Occurrence of Numerous Large Giant Cells in the Tonsils and Pharyngeal Mucosa in Prodromal Stage of Measles By ALFRED SCOTT WARTHIN (Arch of Path, 1931, xi, 864-874.)

This paper, which appeared posthumously, describes an entirely new histopathological feature of the prodromal stage of measles. In four instances, in the course of the examination of about 50,000 pairs of tonsils, there were found a subepithelial infiltration of multinucleate syncytial giant cells, lymphocytes and monocytes, wandering of the giant cells into the mucosa and on to its surface, with edema and congestion, marked lymphoid exhaustion of the germinal centers with production of the multinucleate giant cells from cells of the lymphoblast type and migration of these cells toward the mucosa. In the first patient, two days after tonsillectomy there was a temperature of 102.5° F, coryza, mild conjunctivitis and Koplik's spots. Two days later the fully developed eruption of measles was present. As a result of this experience, when similar giant cells were found subsequently in the tonsils of two other patients, the onset of measles was correctly predicted in advance of any clinical manifestations. In a fourth case, which had been examined without history four years before, a diagnosis of measles was then made, and enquiry brought the information that the patient developed measles on the day following tonsillectomy. These four pairs of tonsils were the only ones in the entire series which showed such giant cells and, as far as known, there were no other instances of prodromal measles in this material. Thus it appears that this pathology is so distinctive that a positive diagnosis of measles can be made from one to five days before the exanthem appears. The process is interpreted as a defensive one, indicating the presence of an etiological agent, either in or on the pharyn-

geal mucosa, but the application of a large variety of staining methods failed to show micro-organisms either in the multinucleate giant cells or in neighboring structures.

Shadows Produced by Lead in the X-Ray Pictures of the Growing Skeleton By EDWARD A. PARK, DEBORAH JACKSON and LASLO KAJDI (Am Jr of Diseases of Child, 1931, vi, 485-499.)

It has been known for some time that the administration of phosphorus to growing children causes the freshly forming trabeculae at the ends of the shafts of the long bones to multiply and become closely packed together, thus producing a dense shadow. After the administration of phosphorus has been suspended for the proper length of time this shadow takes the form of a band which appears displaced toward the shaft since the most recently formed bone at the extremity of the shaft is less dense. In four cases of chronic lead poisoning studied by the authors similar shadows were found, although the bands were not so broad or so striking as those obtained by means of phosphorus. In two fatal cases in young children the shadows were narrow and intense. From this it might be inferred that the period of poisoning was relatively short and the amount of lead ingested large. In the third case the shadow was broad and extended to the cartilage which would indicate that the poisoning had continued to the time of the patient's admission to the hospital. The shadows in the bones in the fourth case were not as intense as the history might lead one to expect but their breadth (1 to 1.5 cm) was in keeping with the known long duration of poisoning, and their position just under the cartilage was in accord with the fact that the eating of lead had continued up to the time when the pictures were taken. It is highly probable that the changes described can occur only in young and growing bones.

and therefore will be the more strikingly developed, the younger the subject. The normal shadows in a child one or two years old or older must not be mistaken for those produced by lead.

The Localizing Significance of Impaired Respiratory Movements in Lesions of the Spinal Cord By WALTER O KLINGMAN (Bull of the Neurol Institute, New York, 191, 1, 136-144)

Information of great value in localizing motor lesions involving the spinal cord may at times be obtained by careful observation of the action of the muscles of respiration. Due regard must be given to non-neurological affections in the thorax which might modify the action of the intercostal muscles and diaphragm. Five groups of variations which are of neurological import are recognized. The *first* group shows exaggerated lateral movements of both costal margins and includes the cases of paralysis of the diaphragm, such as may occur in poliomyelitis and other lesions of the second, third and fourth cervical segments due to syringomyelia, syringobulbia and occasionally infectious myelitis. In the *second* group the entire costal margin of one side moves farther and more promptly in a lateral direction. This indicates a paresis of the diaphragm on the involved side, such as may occur in syringomyelia, localized poliomyelitis and disease of the phrenic nerve. The *third* group exhibits a symmetrical movement of the costal margins of both sides toward the median line and is seen in transverse lesions of the lower cervical and upper thoracic cord, and to a less extent in low lesions of the thoracic cord which interfere with the innervation of the lower six intercostal and the posterior serratus muscles on both sides. The *fourth* group, in which the costal margin of one side moves toward the median line, results from paresis or paralysis of the lower intercostals on the involved side. The costal margin may flare laterally on the opposite side. This has been of value in determining the upper limit of the lesion in acute poliomyelitis. The *fifth* group shows, in addition to the exaggerated lateral

movements of the costal margins, an inspiratory retraction of the upper ribs and manubrium. This occurs with paralysis of the scaleni and upper intercostal muscles and has been observed in the terminal stages of myelitis.

The Specific Therapy of Pneumococcus Type I and Type II Pneumonia By HORACE S BALDWIN (Am Jr Med Sc, 1931, clxxxii, 788-796)

During the four winters of 1926 to 1930 a controlled test of the value of specific therapy in pneumonias due to pneumococcus Type I and Type II has been conducted at the New York Hospital. Patients were assigned to two series in numerical sequence thus establishing an equivalent control group. The concentrated solution containing antibodies for Type I and Type II only, prepared according to the method of Felton, was used. The results were as follows:

Untreated Control Series			
Type	Cases	Died	Per Cent Mortality
I	20	5	
II	29	15	
	—	—	
	49	20	40.8
Treated Series			
Type	Cases	Died	Per Cent Mortality
I	19	1	
II	35	9	
	—	—	
	54	10	18.5

The administration of concentrated immune bodies to these patients was found to be relatively free from dangerous reactions and serum sickness, so that it was possible to give large amounts within a short time. The favorable clinical effect observed seemed to be due largely to the limitation of bacteremia. These results point to a definite advantage derived in specific therapy of Type II pneumonia, hitherto a discouraging procedure, when concentrates of high unit value are given in large amount.

Cinchophen Poisoning By T. P. CHURCHILL and F. H. VAN WAGONER (Proc. Soc. for Exp. Biol. and Med., 1931, xxviii, 581-582)

When rapid cinchophen poisoning was induced in dogs by the administration of 27 times the human therapeutic dose, the animals refused to eat after from two to ten doses had been administered and died in from 9 to 20 days. The blood urea nitrogen first showed a marked rise, followed by a depression before death. The bromsulphalein test showed increased retention of the dye when the urea nitrogen decreased. In certain of the animals acute gastric ulcers were found at autopsy and all exhibited varying degrees of liver damage, from small areas of coagulation necrosis just beneath the capsule to complete disappearance of liver cells in small areas. Two dogs, which had been prepared 11 months before by the production of kidney damage by interference with the renal blood supply, were fed the usual human therapeutic dose of cinchophen, i.e., 22 mg per kilo of weight. The urea nitrogen showed a slight rise, then a slight decrease as the bromsulphalein retention increased. The bromsulphalein test indicated an increasing retention with fluctuation in degree until two feedings were missed when a drop occurred. These dogs survived.

Age Incidence of Communicable Diseases in a Rural Population By EDGAR SYDENSTRICKER and SELWYN D. COLLINS (Public Health Reports, 1931, xlv, 100-113)

The United States Public Health Service, with the cooperation of the Milbank Memorial Fund and the county health department has been conducting epidemiological studies in Cattaraugus County, New York, since 1929. The reports of certain communicable diseases for the preceding period, 1925 to 1929, have also been investigated. These data have been divided according to age, and also according to type of locality, as follows: (a) Cases occurring in Olean, a city of about 22,000, (b) in villages of not over a few hundred population, (c) among persons living on farms, designated as "rural." Measles, scarlet fever and whooping cough were the diseases investigated particularly. It was found that, with hardly an exception, the more rural the population, the higher were the ages at which these diseases occur. In the Olean group there was a marked tendency for a relatively high concentration of these diseases at the ages when children enter school, while in the rural group the risk of attack was more uniformly spread through the ages of childhood and adolescence, and the peak of the curve of incidence came distinctly later in childhood.

Reviews

Practical Treatise on Diseases of the Digestive System By L WINFIELD KOHN, M D, F A C P, Formerly Assistant in the Gastro-Intestinal Clinic, Johns Hopkins Hospital, Baltimore, Chief of the Clinic of Gastro-Enterology, Medico-Chirurgical College, Philadelphia, etc, Present Chief of the Gastro-Intestinal Clinic, Lebanon Hospital, New York City, etc Two volumes, xx + 574, and x + 555 (575 to 1,125) pages, 542 illustrations including 7 colored plates F A Davis Company, Philadelphia, 1930 Price for two volumes, \$12.00 net

Until one surveys the field of essential subject matter that must be included in a treatise on diseases of the digestive system there can be but little realization of the task which confronts the author who attempts such a work. The reviewer might be inclined to be critically disposed when he finds in the present work but a page given over to typhoid fever and only a line to acute poisoning with lead, mercury and arsenic, did he not realize that the entire range of diseases of the alimentary tract, from xerostomia, through the avitaminous diseases to carcinoma of the rectum and hemorrhoids was clamoring for representation. The first chapter is a brief presentation of anatomy of the digestive system, while the second covers the physiology of digestion in 64 pages. The eight chapters which follow give the methods of clinical approach and investigation. Here roentgenological methods receive the most complete discussion, with nearly 100 pages devoted to this division. The author's interest in intragastric photography is shown by a detailed description of the gastro-photor and its uses. Nine pages are given over to reproduction of such photographs. The diseases of the various portions of the digestive system are next taken up in anatomical order and the second volume is brought to a close with chapters

dealing with gastro-intestinal parasites, gastro-intestinal symptoms produced by diseases of other organs, dietary considerations, therapeutic considerations, and a brief discussion of surgery of the gastro-intestinal tract. Brief bibliographies are added to many chapters. This work is very well printed, containing remarkably few typographical errors for a first edition and the division into two volumes adds greatly to convenience in handling. This practical treatise will appeal primarily to physicians engaged in general medicine.

Abdomino-Pelvic Diagnosis in Women By ARTHUR JOHN WALSCHEID, M D, Director of Obstetrical and Gynecological Department of Pan-American Medical Center and Clinics, New York City, Consultant in Gynecology and Obstetrics to Margaret Hague Maternity Hospital, Jersey City, N J, Consulting Gynecologist to Bergen County Hospital, Ridgeway, N J, Consulting Gynecologist to F Reuter Home, North Bergen, N J xxiii + 1,000 pages, 397 illustrations and one color plate. The C V Mosby Company, St Louis, 1931 Price, \$12.50

This work deviates considerably from the usual style of treatises on gynecology. It is strictly limited to the diagnostic field and omits detailed descriptions of normal physiology and anatomy on the one hand, and of operative procedures on the other. It develops the subject along broad anthropologic lines, the author freely acknowledging his debt to Professor Jayles' *Morphology of the Human Female* for this portion of his material. Throughout the entire book this interest in the biological and particularly the psychological phases is apparent. Perhaps the bread-and-butter gynecologists, if there are such, will be disappointed in this method of treatment, for the book must be read with understanding to be appreciated.

The first four chapters, 351 pages, deal with general gynecology, the remainder of the work in ten chapters treats special gynecology, taking up the respective disease conditions in order as determined by anatomical considerations. This section of the book gives less space, relatively, to some of the common, well understood, diseases, and is especially valuable for the completeness with which the less common conditions are treated. The pathologic interpretations are sound and in accordance with the best opinion. A more extended review of this work would be inappropriate for the *ANNALS*. It merits the fullest approval and is especially commended to those who believe that Medicine is, after all, a biological science.

The Treatment of Asthma By A. H. DOUTHWAITE, M.D., F.R.C.P. (Lond.), Assistant Physician, Guy's Hospital, Physician in Charge of Massage Department, Guy's Hospital. viii + 164 pages. William Wood and Company, New York, 1931. Price, \$2.50, net.

The preface of this book states that it is hoped that it presents in an assimilable form all facts and theories of practical importance which are relevant to the subject. Most readers will feel that it falls far short of this goal. One is not led to expect a scientific approach as he reads in the first chapter that the practice of classifying asthmatics according to the apparent etiology or exciting factors is confusing and that such a process really does little to clarify the situation. However, the author does classify causes and his presentation gains thereby. The information presented includes practically none that is new and a bibliography of but 46 items furnishes the list of sources quoted. The discussion of treatment and of the results of treatment is restrained and well balanced. The author is to be commended for his conservatism in refusing to be carried away by any one procedure. Judged by American standards and fashions, this book (printed in Great Britain) is cheaply and unattractively produced. The American purchaser will feel that in respect to both format and content it is overrated.

Physics of Radiology By J. L. WEATHERWAX, M.A., Physicist Philadelphia General Hospital, Associate in Radiotherapeutic Physics, University of Pennsylvania Graduate School of Medicine. 126 illustrations. xviii + 240 pages. Paul B. Hoeber, Inc., New York, 1931. Price, \$5.00.

The older radiologists were able to keep abreast of the development of their subject as their knowledge grew with it in the course of its evolution. For the student who is now entering upon this field of work, the physical problems are far more complex and diversified and the apparatus much more complicated. Without going too deeply into general physics, electricity and mathematics, this textbook presents the necessary information for an understanding of the principles of radiology, the construction of type forms of apparatus, and the general theory of dosage. Thirty-two tables of various constants and other useful information are introduced. The student will find this book of great value in establishing a sound basis of knowledge of the subject. More liberal use of references to the more advanced literature would have been of advantage to the student seeking authority for some of the material presented. The press work is excellent and the binding neat and practical.

Roentgen Interpretation: A Manual for Students and Practitioners By GEORGE W. HOLMES, M.D., Roentgenologist to the Massachusetts General Hospital and Assistant Professor of Roentgenology, Harvard Medical School, and HOWARD E. RUGGLES, M.D., Roentgenologist to the University of California Hospital and Clinical Professor of Roentgenology, University of California Medical School. Fourth edition, revised, xii + 339 pages; 237 illustrations. Lea and Febiger, Philadelphia, 1931. Price, \$5.00, net.

In the interpretation of roentgen pictures, as in the diagnosis of tissue sections, a judgment cannot be made by direct comparison with other pictures or with other slides. Yet such illustrative material may be of very great aid. Each typical process may never be duplicated in respect to all roentgen details, but the changes of the process

eral laws. The authors of this manual have wisely emphasized these principles both in their prefatory advice and in the use of a large number of well chosen illustrations. The first chapter is given over to a brief discussion of confusing shadows and artefacts and the second to anatomical variations and rate of development, with tables giving the time of appearance of the various centers of ossification. This is followed by the pathology of the bones and joints, of the organs of the chest, gastro-intestinal tract and genito-urinary tract. The final section is on fluoroscopic technic. The book is fairly well indexed. The treatment of certain subjects seems inadequate in view of their relative importance. Bronchogenic carcinoma, for instance, is disposed of in one-half page and the discussion starts with the usual statement of the preceding generation of texts, that 'primary malignancy of the lung is rare'. On the whole, however, this book can be heartily recommended. Its careful reading cannot be other than stimulating to the young roentgenologist and to the general practitioner.

Practical Radiation Therapy By IRA I KAPLAN, B S, M D, Director, Division of Cancer, Department of Hospitals, New York City, Attending Radiation Therapist, Bellevue Hospital, Lecturer in Radiation Therapy, New York University and Bellevue Hospital Medical College, Director, New York City Cancer Institute with a chapter on *Applied X-Ray Physics* by CARL B BRAESTRUP, B Sc, P E, Radiation Physicist, Division of Cancer, Department of Hospitals, New York City, Physicist to Mt Sinai Hospital, New York City. 354 pages, 227 illustrations. W B Saunders Company, Philadelphia and London, 1931. Price in cloth, \$6.00.

Chapters on the history, definition and action, and production of x-rays and radium form the introductory material of this book. The last mentioned chapter contains numerous interesting photographs, which are not, however, apropos to the main thesis of the book. Applied x-ray physics then furnishes the necessary background for the discussion

of dosage. The remainder of the book is a description of radiation therapy as practiced at Bellevue Hospital. This portion is excellently illustrated and the pictures are largely left to tell their own story as to the various devices to be employed. The reader must constantly bear in mind that this book is not a guide as to *what* method of treatment is to be used in a particular disease condition, but *how* radiation therapy is to be employed provided it is the method of choice. There are many diseases listed, each with its radiotherapeutic procedure, which most physicians would elect to treat by other methods. Such are salpingitis, gingivitis, glandular hypertrophy of the thyroid, pertussis, asthma, vernal catarrh and nasal polyp. One is prone to wonder what pathologic entity was intended when reference is made to a benign fatty tumor of the thyroid (p 220). This book is well printed, the illustrations are effective. It is sure to be useful to all who are interested in the technical application of radiation therapy.

Microbiology and Elementary Pathology for the Use of Nurses By CHARLES G SINCLAIR, B S, M D, Major, Medical Corps, U S Army, Instructor in Bacteriology, Army Medical School, Instructor in Microbiology and Pathology, Army School of Nursing, Washington, D C. 362 pages, 102 illustrations, some in colors. F A Davis Company, Philadelphia, 1931. Price, \$2.50, net.

The author's experience in instructing student nurses has aided him in selecting for this textbook the essential material and in presenting it in an unusually clear, simple and concise manner. Microbiology occupies 206 pages, Laboratory Exercises in Microbiology, 20 pages, and Elementary Pathology, 103 pages. The last section is perhaps not quite as successful as the others, as it is also the most difficult to present simply to nurses. In each division much skill is shown in the gradual building up of the necessary technical vocabulary, and the presentation is aided by the many well chosen illustrations. This should prove to be a very useful and satisfactory book for the field for which it is intended.

College News Notes

ABSTRACT OF MINUTES OF THE MEETING OF THE BOARD OF REGENTS, Philadelphia, Pa., June 9, 1931.

The Board of Regents of the American College of Physicians met at the College Headquarters in Philadelphia, June 9, 1931, with the following present President S. Marx White, Drs David P Barr, Walter L. Bierring, Charles G Jennings, Clement R Jones, James S McLester, James H. Means, James Alex Miller, Sydney R Miller, John H Musser, O H Perry Pepper, George Morris Piersol, Maurice C Pincoffs, Francis M Pottenger, and Mr E R Loveland, Executive Secretary.

President S Marx White spoke briefly about College affairs, referring especially to the death of Dr Aldred Scott Warthin, and the necessity of action by the Board of Regents in providing for the future continuation of the journal, *ANNALS OF INTERNAL MEDICINE*.

The Executive Secretary reported the deaths of nine members since the preceding Regents' meeting, presented special cases requiring action by the Board in respect to fees and dues, and reported in detail the gifts of books and publications presented to the College Library by members, etc. A resolution was adopted providing that Dr. Donald J Frick, of Los Angeles, and Dr. John E Heatley, of Oklahoma City, should be reinstated as Fellows of the College.

Upon the report of the death of Dr Reynold Webb Wilcox on June 6, 1931, the following resolution was adopted:

Resolved, that the Secretary-General should be instructed to draw up a proper resolution concerning Dr Reynold Webb Wilcox, in recognition of his being the first President of the American College of Physicians.

Upon report of the death of Dr Aldred Scott Warthin on May 23, 1931, in recognition of his eminent contributions to the College through the Editorship of the Journal, the following resolution was adopted:

Resolved, that a Committee be appointed to draw up a suitable resolution concerning Dr. Aldred Scott Warthin for publication in the *ANNALS OF INTERNAL MEDICINE*.

Dr George Morris Piersol, Chairman of the Committee on Credentials, presented the report of his Committee, recommending the election of the following named candidates, who, upon resolution regularly adopted, were elected Fellows of the College.

(The following list is arranged geographically with respect to the candidates elected. Under each candidate's name are listed (1) name of proposer, (2) name of second, and (3) name of endorser.)

CALIFORNIA

San Francisco

- Stacy Raymond Mettier
1 William J. Kerr
2 Ernest H Falconer
3 Hans Lisser

COLORADO

Denver

- Matthew A Spangelberger
1 P. J. Potluisje
2 T R Love
3 J N. Hall

DISTRICT OF COLUMBIA

Washington

- Frederick Ceres (M C, U.S N)
1 Joel J White
2 F. F. Murdoch
3 William Gerry Morgan
and
Charles E. Rippa
Robert Copeland McCreary
1 Donald C. Smith
2 L. G. P. Vane
3 Walter C. Gerry Morgan

FLORIDA

Jacksonville

Clayton Elbert Royce

- 1 William W Kirk
- 2 R H McGinnis
- 3 T Z Cason

Lake City

Harold Foor Machlan

1. Louis Hamman
- 2 Sydney R Miller
- 3 T Z Cason

GEORGIA

Atlanta

Millard Everingham Winchester

- 1 Joe P Bowdoin
- 2 T F Abercrombie
- 3 Allen H Bunce
and
Russell H Oppenheimer

Macon

Fred Leland Webb

- 1 M A Clark
- 2 Allen H Bunce
- 3 Russell H Oppenheimer

Millen

Guy George Lunsford

- 1 Joe P Bowdoin
- 2 T F Abercrombie
- 3 Allen H Bunce
and
Russell H Oppenheimer

Savannah

J Reid Broderick

- 1 Lee Howard
- 2 Ralston Lattimore
- 3 Russell H Oppenheimer

ILLINOIS

Rockford

Robinson Bosworth

- 1 Clarence H Boswell
- 2 Anna Weld
- 3 James G Carr

IOWA

Council Bluffs

Aldis Adelbert Johnson

- 1 John H Peck
- 2 A C Page
- 3 Tom B Throckmorton
and
Walter L Bierring

Des Moines

John Thomas Strawn

- 1 A C Page
- 2 John H Peck
- 3 Tom B Throckmorton
and
Walter L Bierring

Independence

Judd Campbell Shellito

- 1 Elmer G Senty
- 2 John I Marker
- 3 Walter L Bierring

Mason City

Lee Roy Woodward

- 1 Daniel J Glomset
- 2 John H Peck
- 3 Tom B Throckmorton
and
Walter L Bierring

KENTUCKY

Louisville

Hugh Rodman Leavell

- 1 C W Dowden
and
William E Gardner
- 2 Charles G Lucas
and
J Rowan Morrison
- 3 Ernest B Bradley

MARYLAND

Baltimore

Ernest Howard Gaither

- 1 Thomas R Brown
- 2 Sydney R Miller
- 3 Henry M Thomas, Jr

MASSACHUSETTS

Boston

James Morison Faulkner

- 1 George R Minot
 - 2 Soma Weiss
 - 3 Roger I Lee
- Harry Winfred Goodall
- 1 Maurice Fremont-Smith
 - 2 William B Breed
 - 3 James H Means
and
Roger I Lee
- Francis Cooley Hall
- 1 William B Breed
 - 2 Maurice Fremont-Smith
 - 3 Roger I Lee

Howard Burnham Sprague

- 1 Paul D White
- 2 William B Breed
- 3 J H Means
and
Roger I Lee

Brookline

Walter Bauer

- 1 Dwight L Siscoe
- 2 Chester M. Jones
- 3 J H Means
and
Roger I. Lee

NEW HAMPSHIRE

Manchester

Hetnry W N Bennett

1. Robert B Kerr
- 2 Louis O S Wallace
- 3 Edward O Otis

NEW JERSEY

Asbury Park

Joseph H. Bryan

- 1 Clarence M Trippe
- 2 James J McGuire
3. W. Blair Stewart

Frechold

Warren H. Fairbanks

- 1 Clarence M Trippe
- 2 William G Herrman
- 3 W Blair Stewart

Union City

Charles Vincent Niemeyer

1. Abraham E Jaffin
- 2 Eugene J Luippold
- 3 W. Blair Stewart

NEW YORK

New York

Walter Palmer Anderton

- 1 Frank Bethiel Cross
- 2 W W Herrick
- 3 James Alex Miller
and

Luther F Warren

Robert Chobot

- 1 Luvia M Willard
- 2 Robert A Cooke
- 3 James Alex Miller
and
Luther F. Warren

Isidore William Held

- 1 Harlow Brooks
- 2 I Seth Hirsch
- 3 Luther F Warren

Samuel Waldron Lambert

1. Warren Coleman
- 2 Harlow Brooks
- 3 Luther F Warren

Josephine Bicknell Neal

- 1 Luvia M Willard
- 2 Harlow Brooks
- 3 James Alex Miller
and

Luther F Warren

Willard Cole Rappleye

- 1 Luther F Warren
- 2 James Alex Miller
3. Walter L Bierring

Poughkeepsie

Scott Lord Smith

- 1 W. W. Herrick
- 2 Frank J. Sladen
- 3 Harlow Brooks

Richmond Hill

Frank J. Weigand

- 1 Ernest E Keet
- 2 Luvia M Willard
- 3 James Alex Miller
and
Harlow Brooks

NORTH CAROLINA

Raleigh

Hubert Benbury Haywood

- 1 William de B MacNide
- 2 William B. Dewar
- 3 C H. Cocke

Winston-Salem

Wingate Memory Johnson

- 1 Thurman D Kitchin
- 2 L. B. McBrayer
- 3 C H Cocke

OHIO

Cincinnati

Mark Atkins Brown

- 1 Roger S Morris
2. William I. Freyhof
- 3 James S. McLeiter
and
A B Brown

PENNSYLVANIA

Philadelphia

James Craig Small

- 1 Frank Walton Burge
- 2 Robert G Torrey
- 3 E J G Beardsley

Pittsburgh

George Jacob Kastlin

- 1 Ellis M Frost
- 2 C Howard Marcy
- 3 E Bosworth McCready

WEST VIRGINIA

Morgantown

George Ralph Maxwell

- 1 Edward J Van Liere
- 2 Martin L Bonar
- 3 John N Simpson

WISCONSIN

Milwaukee

Roy Wilmot Benton

- 1 Theodore L Squier
- 2 John Huston
- 3 Rock Sleyster

CANADA

Ontario

Toronto

George Chambers Anglin

- 1 W. E Ogden
- 2 A H Caulfeild
- 3 Jabez H Elliott

Quebec

Montreal

Colin George Sutherland

- 1 C F Martin
- 2 R H M Hardisty
- 3 S Sclater Lewis

Henry Pulteney Wright

- 1 C F Martin
- 2 Arthur T Henderson
- 3 D Sclater Lewis

Dr Clement R Jones, Treasurer, presented a trust agreement between the American College of Physicians and the Bank of Pittsburgh National Association, providing a means of the bank acting as trustee of the securities of the American College of Physicians, in accordance with a resolution adopted during the Baltimore Clinical Ses-

sion in March. The College has set aside \$50,000 as the nucleus for an Endowment Fund, to which shall be added direct subscriptions for Life Membership, gifts of funds, and bequests in connection with estates. The principal shall be kept intact, and invested in bonds approved by the Board of Regents. By resolution, the Secretary-General, Dr George Morris Piersol, and the Treasurer, Dr Clement R Jones, were instructed to complete the trust agreement with the Bank of Pittsburgh National Association, in accordance with directions and recommendations made by the Board of Regents.

New regulations for the John Phillips Memorial Prize, as printed below, were reviewed, and the following Committee appointed and instructed to proceed in accordance therewith:

James H Means, Chairman, Boston, Mass
David P Barr, St Louis, Mo

James S McLester, Birmingham, Ala
Jonathan C Meakins, Montreal, Que
John H Musser, New Orleans, La

Revised Regulations

JOHN PHILLIPS MEMORIAL PRIZE

- I (a) Interpretation of Internal Medicine—This term should include not only Clinical Science, but, in addition, all those subjects which have a direct bearing upon the advancement of Clinical Science,
- (b) The work upon which this is based must have been done in whole or in part in the United States or Canada
- II Not less than two or more than three members of the Committee should be reappointed each year,
- III (a) The Committee shall appoint Fellows of the College who shall each maintain a close contact with a particular field of the realm of Medical Science and shall report to the Committee any specially meritorious work which has been accomplished in this field,

- (b) If considered necessary or desirable the Committee may appoint a small Board of Referees to visit (at the expense of the College) a particular investigator whose work appears to be of sufficient merit, in order that a first-hand opinion may be obtained by competent observers
- (c) The Committee, after due consideration of the reports submitted by the above appointed Fellows and Referees, may select a recipient or recipients for the Prize and should inform the President of their choice at least two months before the date of the Annual Meeting
- (d) The College reserves the right to make no award of the Prize if a sufficiently meritorious piece of work has not been recommended

IV The recipient of the Prize will be expected to file with the College a written account of his work and to present his results as a paper before the next Annual Meeting after which he will be officially presented with the Prize by the President

- V (a) The announcement of the Prize-Winner will be made not later than two months before the Annual Meeting of the College
- (b) The Executive Secretary shall inform the recipient of the Prize that the College would be pleased to defray his transportation expenses when he attends the Annual Meeting to receive the Prize

President White reported upon arrangements being made for the General Program of the San Francisco Clinical Session to be held April 4-8, 1932. As President of the College, Dr. White is responsible for the preparation of the program of the General

Scientific Sessions. Dr. White reported that he had asked Dr. William J. Kerr, of San Francisco, Dr. Noble Wiley Jones, of Portland, and Dr. F. M. Pottenger, of Monrovia, in conjunction with other men, to act as an Advisory Committee and give names of the men from the far West whose work is desirable for presentation. As a result, a large amount of excellent material has been offered and will be used to make up a considerable proportion, less than half, of the program for the General Sessions in San Francisco next April. Dr. White reported that he has planned, as a feature of the General Program, a scientific presentation of the sympathetic nervous system. The Board of Regents authorized him to invite some outstanding foreign guest on this subject, the name of Dr. Dale, of London, being prominently mentioned.

Dr. F. M. Pottenger reported that all local arrangements have been made for the San Francisco meeting, by Dr. Kerr and his several Committees, and that Dr. Kerr, as General Chairman, expects to have the complete program of clinics ready to submit in late August or early September. Dr. Pottenger also referred to a program of entertainment which the members of the College in Southern California, especially around Los Angeles, are arranging after the San Francisco Session.

Mr. E. R. Loveland, Executive Secretary, reported that he had made a trip to San Francisco and Los Angeles, in accordance with directions of the Regents, and that he, with the assistance of Doctors Pottenger and Kerr, had completed business arrangements for the 1932 Clinical Session. The Palace Hotel has been selected not only for hotel headquarters, but for general headquarters for registration, general scientific sessions, exhibits, etc. Railroad fares on the Certificate Plan of reduced rates will apply to all physicians and members of their families attending the Session. A special train will be operated from the East through to San Francisco, leaving there immediately after the Session taking members through the Yosemite Valley to Los Angeles and thence by way of the Grand Canyon back East. It is anticipated that the reduced fares will entitle members to optional return routes.

The Executive Secretary reported that the 1931-1932 Directory of the College will be ready for distribution about September 1

President White paid tribute to the late Dr Warthin by saying in part, "Dr Warthin's service to the College has been such an outstanding one, his Editorship of the Annals has been so acceptable and the Annals has been taking such a prominent place in Medical literature that his death leaves a serious loss"

A special Committee consisting of Dr S Marx White, Dr George Morris Piersol and Dr David P Barr was appointed with instructions to function immediately with respect to carrying on the Annals, to survey the situation with respect to a new Editor and an Editorial Board, to make recommendations concerning the manner in which the Journal should be managed, and to bring back recommendations to the next meeting of the Board of Regents

Upon motion by Dr Maurice C Pincoffs, seconded by Dr David P Barr, and regularly carried, it was

RESOLVED, the President shall appoint a Committee on Public Relations to which shall be referred all matters affecting the College or the medical profession in its relation to the public This Committee shall report its recommendations to the Board of Regents for approval or action The Committee shall consist of four members with the President a member ex officio, the terms of office shall be so arranged that one new member shall be appointed each year, with a maximum term of four years

President White appointed the following Committee on Public Relations

Charles G Jennings, Chairman	4 years
Walter L Bierring	3 years
James Alex Miller	2 years
W Blair Stewart	1 year
S Marx White (President, ex officio)	
Adjournment	

DOCTOR ALFRED STENGEL

Dr Alfred Stengel (Master), Philadelphia, was appointed Vice President of the University of Pennsylvania, in charge of medical affairs, at the annual Commencement of that institution on June 17 Through Dr

Stengel's appointment, the University of Pennsylvania plans a coordination of all the existing schools and departments included in the medical, dental, hygiene, veterinary and physical educational work This will embrace the University of Pennsylvania School of Medicine, the Graduate School of Medicine, the Phipps Institute, the Wistar Institute, the University Hospital, Graduate Hospital, the Orthopedic Hospital and the Institute of Mental Health of the Pennsylvania Hospital

Dr Stengel is a graduate of the University of Pennsylvania School of Medicine, and has been connected with the medical faculty since 1893 He is at present Professor of Medicine, both in the School of Medicine and in the Graduate School of Medicine; he is a term trustee of the University of Pennsylvania, a member of the Trustees' Executive Board, a member of the Trustees' Board of Medical Affairs, and a member of the Managing Committee of the University of Pennsylvania Fund On the occasion of the 165th anniversary of the founding of the School of Medicine last year, Dr Stengel was awarded the honorary degree of Doctor of Laws He also holds the degree of Doctor of Laws from Lafayette College and the degree of Doctor of Science from the University of Pittsburgh

Dr Stengel was President of the American College of Physicians for two successive years, 1925-1926 and 1926-1927 He has rendered distinguished service to the College for many years, and was made a Master during the Boston Clinical Session in 1929

Announcement is made of the prospective organization of an Association among those seeking post-graduate courses in Medicine given in English in Berlin With this Association the present Dozentenverein of the University of Berlin will cooperate The general plan contemplates an organization similar to the well-known American Medical Association of Vienna Inquiries and applications may be addressed to the organizing secretary, Miss Anny Engel, whose present address is Vienna I, Bösendorferstrasse 6, Austria

COLLEGE LIBRARY OF PUBLICATIONS BY MEMBERS

Members of the College are urged to contribute copies of books of which they are authors or co-authors to the College Library. The following Fellows recently contributed the books named

Dr James S McLester (Fellow), Birmingham, Ala

"Nutrition and Diet in Health and Disease"

Dr. Bernard L Wyatt (Fellow), Tucson, Ariz

"Chronic Arthritis and Rheumatoid Affections"

Dr Edwin Henes, Jr (Fellow), Milwaukee, Wisc

"Minneapolis Proceedings of the Interstate Postgraduate Medical Association of North America"

In addition to the above gifts, acknowledgment is made of the receipt of a considerable number of reprints, from the following members.

Dr Jacob M Cahan (Fellow), Philadelphia, Pa—8 reprints,

Dr Gustave P Grabfield (Fellow), Boston, Mass—20 reprints,

Dr. A Morris Ginsberg (Fellow), Kansas City, Mo—I reprint,

Dr Earle E Mack (Associate), Syracuse, N Y—I reprint;

Dr. Philip B. Matz (Fellow), Washington, D C—2 reprints,

Dr. Carl V. Vischer (Fellow), Philadelphia, Pa—I reprint;

Dr Joseph R Darnall (Fellow), Riverdale, Md—I reprint;

Dr. George R. Minot (Fellow), Boston, Mass—13 reprints,

Dr. Aaron E Parsonnet (Fellow), Newark, N J, with Dr. Albert S. Hyman (Fellow), New York, N. Y—4 reprints;

Dr. William D Reid (Fellow), Boston, Mass—2 reprints;

Dr John M. Swann (Fellow), Rochester, N. Y—19 reprints;

Dr. C F Tenney (Fellow), New York, N. Y—3 reprints,

Dr Robert A C Wollenberg (Fellow), Detroit, Mich—I reprint,

Dr. Bernard L Wyatt (Fellow), Tucson, Ariz—5 reprints

At the 64th annual meeting of the West Virginia State Medical Association, held at Clarksburg, May 19-21, contributions were made to the program by the following members of the College

Dr Sydney R. Miller (Fellow), Baltimore, Md—"Arthritis",

Dr W. H Mayer (Fellow), Pittsburgh, Pa—"The Nervous Patient and the General Practitioner";

Dr. John N Simpson (Fellow), Morgantown, W Va—"What the Medical Department of West Virginia University Has Accomplished Since its Inception",

Dr. Howard T Phillips (Fellow), Wheeling, W. Va—"Ringworm Infection of the Hands, Feet and Groins";

Dr Albert H. Hoge (Fellow), Bluefield, W. Va—"Hypothyroidism as a Cause of Chronic Infection",

Dr Ray C. Blankinship (Fellow), Madison, Wis—"Medical Aspects of Jaundice",

Dr. G H Barksdale (Associate), Charleston, W Va—"Oration on Medicine"

Dr. James B Herrick (Fellow), Chicago, delivered the Abner Welborn Calhoun Lecture on "Common Errors in the Treatment of Heart Disease" at the eighty-second annual session of the Medical Association of Georgia, held at Atlanta, May 12-15.

Dr. William Gerry Morgan (Fellow), Washington, D. C., President of the American Medical Association, also delivered an address

Col Charles R. Reynolds (Fellow), Carlisle Barracks, Pa, delivered the chief address on field training for medical officers at the annual conference of the medical subchapter of the Cook County (Ill) Chapter of the Reserve Officers Association, U. S. Army, at Chicago, on May 18

Dr. Benjamin Goldberg (Fellow), Chicago, has resigned as Medical Director of

the Chicago Municipal Tuberculosis Sanitarium

Dr Thomas Addis (Fellow), Professor of Medicine, Stanford University Medical School, San Francisco, delivered the fourth course of lectures under the William Sydney Thayer and Susan Read Thayer Lectureship in Clinical Medicine in the School of Hygiene and Public Health of the Johns Hopkins University School of Medicine, Baltimore, May 11 and 12. The title of his first lecture was "The Natural History of Glomerular Nephritis," and the second lecture, "Questions in Connection with the Prognosis, Treatment and Etiology of Glomerular Nephritis"

Dr James B Bullitt (Fellow), Chapel Hill, N C, delivered the annual oration on "State Medicine" before the sixty-fourth annual meeting of the Mississippi State Medical Association, held at Jackson, May 12-14

Dr Edward O Otis (Fellow), Exeter, N H, was the recipient of a gold medal for fifty years of membership in the New Hampshire State Medical Association at its annual meeting in Manchester, May 19-20. Dr Otis has long been an enthusiastic, influential and active worker in New England medical organizations, as well as in many national societies

Dr William Gerry Morgan (Fellow), Washington, D C, delivered two addresses during the New Hampshire Medical Society's annual meeting

Dr Paul D White (Fellow), Boston, and Dr George Blumer (Fellow), New Haven, were also guest speakers, their titles being "Significance and Treatment of Cardiac Symptoms and Signs" and "Coronary Occlusion and Angina Pectoris," respectively

The following Fellows contributed articles indicated in the June Issue of the American Journal of the Medical Sciences

Dr James H Means (Fellow), Boston, Mass (with Lerman)—"Iodine in Exophthalmic Goiter. A Comparison of the

Effect of Ethyl Iodide and Potassium Iodide with that of Lugol's Solution", Dr Louis P Hamburger (Fellow), Baltimore, Md—"Head Murmurs"

Dr I S Trostler (Fellow), Chicago, recently addressed the LaPorte County (Ind) Medical Society

Dr Trostler also presented a paper on "Roentgenotherapy in Benign Diseases" before the Illinois State Medical Society at East St Louis, Ill, on May 6, a paper entitled "A Few Interesting X-Ray Findings with Clinical Summaries" before the North Side Branch of the Chicago Medical Society, May 14, and a paper on "Reports on Roentgen Findings" before the Section on Radiology of the American Medical Association at Philadelphia on June 11

Dr Maximilian J Hubeny (Fellow), Chicago, recently officiated as Toastmaster at the banquet of the Wisconsin State Medical Society, Section on Radiology, at Milwaukee

The Radiological Society of North America will hold its 17th annual meeting at the New Jefferson Hotel, St Louis, Mo, November 30 to December 5, 1931

Dr Edwin C Ernst (Fellow), St. Louis, acted as Secretary of the American Delegation to the Third International Congress on Radiology, which was held in Paris during July

Dr Benjamin H Orndoff (Fellow), Chicago, presented a paper on "The Treatment of Breast Carcinoma" before the Section on Radiology of the Illinois State Medical Society's meeting on May 7

Dr Harold Swanberg (Fellow), Quincy, Ill, is Secretary of the Secretaries' Conference of the Illinois State Medical Society

Dr Louise Tayler-Jones (Fellow), Washington, D C, is Vice President of the Medical Women's International Association, which represents twenty-two countries. Dr

Taylor-Jones will attend the next meeting of this organization in Vienna during September

Dr Elizabeth Bass (Fellow), New Orleans, La, Dr Martha Tracy (Fellow), Philadelphia, and Dr. Louise Taylor-Jones (Fellow), Washington, D C, each contributed articles to the March issue of the Medical Review of Reviews

Dr Arthur Bloomfield (Fellow) and Dr Walter W Boardman (Fellow), both of San Francisco, Calif, presented a very interesting clinic on gastro-intestinal diseases before the California Medical Association's meeting in May

Dr. Clyde Brooks (Fellow) has resigned as Professor of Physiology and Chairman of Research at the University of Alabama to accept an appointment as Head of Physiology and Pharmacology of the new medical center which is being developed on the campus of Charity Hospital, New Orleans, under the auspices of the Louisiana State University

The new medical school, at the beginning, will have a first year and a third year class of medical students opening this autumn. Dr. Aristides Agramonte, of Havana, has accepted the appointment as Head of the Department of Tropical Diseases

Dr Grafton Tyler Brown (Fellow) and Dr Oscar B Hunter (Fellow), Washington, D C, were contributors to the Allergy Exhibit at the Philadelphia meeting of the American Medical Association. Their contribution consisted of an exhibit of fungi (molds and yeasts) in relation to allergic conditions

Dr Brown presented a paper on 'Maximum Dosage in Pollen Therapy' at the Ninth Annual Meeting of the Association for the Study of Allergy in Philadelphia on June 9

Dr. Roy H. Clark (Fellow), Philadelphia, is the Gerald H. Lecturer on the Future Course Medical Society at Union College, Schuylkill, Pa. May 16

Dr. Clark's presentation was a study

of graduate instruction given by the Medical School of the University of Michigan at Ann Arbor, lecturing the entire day of May 20

Dr Harold S Davidson (Fellow), Atlantic City, N J, made the address of welcome to the American Therapeutic Society's meeting in Atlantic City, June 5-6

Dr Clement R Jones (Fellow), Pittsburgh, Pa, is President, Dr Grafton Tyler Brown (Fellow), Washington, is Secretary, and Dr Truman G Schnabel (Fellow), Philadelphia, is Treasurer

Dr Joseph C Doane (Fellow), Associate Professor of Medicine, Temple University of Philadelphia, and Associate Professor of Medicine, Graduate School of Medicine, University of Pennsylvania, recently spoke before a joint meeting of the Fifth Councillor District of the State Medical Society of New Jersey and the Atlantic County Medical Society at Atlantic City, N J, on the subject "What the Public Thinks of the Present Day Practice of Medicine", Dr Doane addressed the Philadelphia College of Physicians recently on "Some Observations on the Study of the Results of One Hundred and Seventy-five Post Mortem Examinations", and again the Atlantic County Medical Society, May 8, on "Diseases of the Endarteries"

Dr Benjamin Hobson Frayser (Fellow) has recently been transferred from the U S Veterans' Hospital at Fort Harrison, Mont to the U S Veterans' Hospital at Lexington, Ky

Dr Harry Gauss (Fellow), Denver, Colo, addressed the Medical Society of the City and County of Denver, May 18, on 'The Etiology and Management of Chronic Diarrhea'

The C V Mosby Company, of St Louis, has recently published in book form "Clinical Dietetics"

A new contributor to the program of the Blue Star Medical Society will be Dr. H. S. Jones of May 16, 1934

Fellows, not previously mentioned, are included

Dr Andrew C Ivy (Fellow), Chicago—"Facts Concerned in Gall Bladder Evacuation",

Dr Nathan S Davis, III (Fellow), Chicago, Secretary of the Chicago Medical Society—"Public Relations of the County Medical Society"

Dr William H Kraemer (Fellow), Wilmington, Del, addressed the Faculty Club of the University of Delaware, at one of its recent monthly meetings, on "Some of the Leading Problems in Medical Research of the Present Day"

Dr Kraemer also addressed the Commission on Cancer of the State of Pennsylvania at the Moses Taylor Hospital on the subject, "The Medical Treatment of Cancer"

Dr Kraemer is Director of the Tumor Clinic of the Jefferson Hospital of Philadelphia. The Tumor Clinic was founded through the creation of the "Elizabeth Storck Kraemer Memorial Fund," through the contributions by Mr Pierre S de Pont of \$25,000 for furniture and apparatus, \$10,000 additional toward fitting up the Department, and \$10,000 annually for five years toward the expenses of the practical work of the Clinic. Mr Lamot du Pont also contributed \$15,000 toward the support of the work of the Clinic. "The object of this clinic is research for the advancement of the knowledge of cancer along lines of surgery, x-ray, radium and chemical compounds, such as lead, which study has been pursued actively at Jefferson Hospital during the last two years"

Dr John I Marker (Fellow), Davenport, Iowa, addressed the St Louis Medical Society, Duluth, Minn, June 11, on "The County Contract for Care of the Indigent"

At the meeting of the National Tuberculosis Association at Syracuse, N Y, during May, Dr P P McCam (Fellow), Sanatorium, N C, was re-elected for a two-year term on the Board of Directors, and Dr L B McBrayer (Fellow), Southern Pines, N C, was re-elected to membership on the Committee of Health Education

The following Fellows of the College are members of the Board of Directors of the North Carolina Tuberculosis Association

Dr Paul Ringer, Asheville,
 Dr P P McCam, Sanatorium,
 Dr M L Stevens, Asheville,
 Dr S D Craig, Winston-Salem,
 Dr W B Kinlaw, Rocky Mount,
 Dr William H Smith, Goldsboro,
 Dr L B McBrayer, Southern Pines

Dr Robert M Moore (Fellow), Indianapolis, recently addressed the Tenth District Medical Society at East Chicago, and the Hancock County Medical Society at Fortville, his subjects being "The Heart in Surgery" and the "Management of Certain Types of Cardiac Cases," respectively

Dr Samuel E Munson (Fellow), Springfield, Ill, was recently re-elected Councilor of the Fifth District of the Illinois State Medical Society for three years. Dr Munson has held this office since 1925

Dr Oliver T Osborne (Fellow), New Haven, Conn, has been nominated to the "Hall for Famous Men" of The Heckscher Institute for Child Health, New York City

Dr Curran Pope (Associate), Louisville, Ky, delivered a radiophone address on May 5 over station WLAP, at Louisville, under the auspices of the Woman's Auxiliary of the Jefferson County Medical Society, his subject being "The Conservation of Nervous Energy"

Dr Pope was a guest of the West Virginia State Medical Association at their annual meeting in Clarksburg, W Va, May 19-21. Dr Pope discussed a number of papers on the program, and also delivered an address at the luncheon of the Rotary Club

At the annual meeting of the Board of Trustees of Syracuse University in May, the following promotions were made in the faculty of the College of Medicine: Edward C Reifenshein (Fellow) to Professor of Medicine, Maynard E Holmes (Fellow) to Assistant Professor of Clinical Medicine

Dr David Riesman (Fellow), Philadelphia, was elected President of the American Association of the History of Medicine at its recent meeting in Atlantic City

Dr Raymond W Swinney (Fellow) has removed from Kansas City, Mo, to Long Beach, Calif

Dr Carl V Vischer (Fellow), Philadelphia is co-author with Dr Thomas J Vischer (Associate), Philadelphia, of an article in the May Hahnemannian Monthly, "The VonPirquet Test, its Value as an Aid in the Diagnosis of Tuberculous Infection"

Dr Conrad Wesselhoeft (Fellow), Boston, was appointed Associate in Communicable Diseases, Department of Pediatrics, Harvard University Medical School, on June 3

"Forty Years as a Clinical Pathologist" was the title of a paper that appeared in the May, 1931, Issue of the Journal of Laboratory and Clinical Medicine under the authorship of Dr Aldred Scott Warthin (Master), Ann Arbor, Mich, now deceased

Dr Carl H Greene (Fellow) and Dr Albert M Snell (Fellow) (with Walters), Rochester, Minn, contributed an article to the same journal entitled "Functional Tests in the Surgical Diagnosis and Treatment of Diseases of the Liver and Bile Ducts"

Dr Henry J John (Fellow), Cleveland, also contributed an article on "Surgery in the Presence of Diabetes"

In the June issue of Radiology, the following Fellows contributed articles

Dr Thomas A Groover, Washington, D C—"Radiology as a Career",

Dr. L J Carter, Brandon, Man, Canada—"The X-Ray Treatment of Essential Heartburn",

Dr. L S Trostler, Chicago, Ill—"An Obscure Bone Case"

An important guest is listed in the preliminary program for the graduate conference which will be held at the University of Illinois, Urbana, June 15 to 20

appeared the names of the following Fellows

Dr W W Duke, Kansas City, Mo

Dr William Engelbach, New York, N. Y

Dr L G Rowntree, Rochester, Minn

Dr B B Vincent Lyon (Fellow), Philadelphia, addressed the Medical Society of New Jersey at Asbury Park, June 3 to 5, on "Value of Duodenal Tube Drainage of the Biliary System and Treatment of Various Diseases and Disorders of the Liver"

Dr Elias H Bartley (Fellow), Brooklyn, recently retired as President of the Medical Board of the Kingston Avenue Hospital for Contagious Diseases Dr Bartley was a member of the Board for thirty years, and President for fifteen years

Dr Otis S Warr (Fellow), Memphis, addressed the West Tennessee Medical and Surgical Association, May 20 to 22, on "Undulant Fever"

At the annual meeting of the Medical Society of the District of Columbia, May 6-7, the following Fellows of the College took part

Dr William Gerry Morgan, Washington—"Some of the Medicinal Effects of Alcohol",

Dr Walter Freeman, Washington—"Malaria Treatment of Neurosyphilis",

Dr Alexander B Moore, Washington—"Gastro-intestinal Bleeding",

Dr J Russell Verbruycke, Jr, Washington—"Cardiospasm"

Dr Arthur C Christie (Fellow), Washington, was elected President, Mary O'Malley (Fellow), Washington, one of the Vice Presidents, and Dr Coursen B. Conklin (Fellow), Washington, was re-elected Secretary

Dr Cecil M Jack (Fellow), Decatur, Ill, addressed the Adams County Medical Society at Quincy, Ill May 11, on "Value of an Observational Station in a Tuberculous Sanatorium"

Dr John H. H. (Fellow), Chicago, addressed the Chicago Medical Association

ciet, May 11, on "Premature Infants as a Present-Day Problem"

Dr J A Barga (Fellow), Rochester, Minn, addressed the Pennsylvania Radiological Society, May 13 to 14, at McKeesport on "Clinical and Radiological Aspects of Chronic Ulcerative Colitis"

Dr Marr Bisailon (Fellow), Portland, Ore, used as his subject "Differential Diagnosis of Malignancy of the Lung" in an address, May 4, before the King County (Washington) Medical Society

Dr Charles James Bloom (Fellow) addressed the St Tammany Parish Medical Society, June 12, 1931, on "Intestinal Disturbances in Infants and Children"

Dr Louis F Bishop (Fellow) and Dr Louis F Bishop, Jr (Fellow) addressed the American Therapeutic Society at Atlantic City, June 5, 1931, on "A Study of Cardiovascular Syphilis in Private Practice"

Dr G L Pinney (Fellow), Hastings, Nebraska, has been elected Delegate to the State Medical Meeting for the third successive year. At that meeting, May 14, he read a paper on "Cardiac Hypertrophy"

Dr Leon T LeWald (Fellow), Professor of Roentgenology, New York University and Bellevue Hospital Medical College, read a paper entitled "Gastric Les, Roentgen Diagnosis and Differential Diagnosis from Gastric Ulcer and Carcinoma" before the Connecticut State Medical Society at Bridgeport, Conn, on May 20th, 1931

OBITUARY

DOCTOR FRANCIS XAVIER
DERCUM

Dr Francis Xavier Dercum, world-famous neurologist, died suddenly on April 23, 1931, a few minutes after the closing of the executive session of the American Philosophical Society. As president of the Society he had read his report and was about to open formally the 204th Annual Meeting when the end came. Seated in the chair of Benjamin Franklin, the founder, in the presence of an audience made up of distinguished scientists and surrounded by trophies of America's scientific progress over the last two centuries, an impressive and dignified setting completely symbolic of his distinguished career, he suddenly collapsed and passed away without regaining consciousness. "He died," remarked a fellow-scientist, "as a scientist would wish."

Born in Philadelphia, August 10, 1856, a son of Ernest Albert and Susanna Elhart Dercum, Dr Dercum attended the public schools of his native city and was graduated from the Central High School in 1873. At an early age Dr Dercum resolved to study medicine and in 1877 was graduated from the Medical Department of the University of Pennsylvania and in that year also won a Ph.D. from the same institution. While a student in the medical school, he devoted attention to scientific investigation and following his graduation this interest became a dominant attribute of Dr Dercum. Although he continued to work for a number of years in the laboratory of the University of

Pennsylvania, he at once became a member of the Academy of Natural Sciences, Philadelphia, to which he made original contributions from time to time. In 1878 his ability as an anatomist was recognized by his appointment as an assistant demonstrator in the histologic laboratories under Dr Richardson, and very soon thereafter he was appointed demonstrator in the laboratory of physiology under Professor Harrison Allen. Here he demonstrated practical histology, fungi, algae, protozoa, and bacteria, "thus obtaining a solid foundation in what was then the new science of bacteriology."

In 1883, at the request of his friend and former teacher, Dr Horatio C. Wood, he directed his scientific studies to nervous diseases. Almost simultaneously he was appointed Chief of the Nervous Dispensary and Instructor of Nervous Diseases in the medical school of the University of Pennsylvania. While Dr Dercum was holding this position, Muiybridge began his studies of the movements of horses in the open lot behind the University Hospital. Muiybridge also photographed for Dr Dercum men exhibiting normal and pathological gait as well as persons in convulsions. In order to get pictures of persons in convulsions Dr Dercum would induce them artificially by suggestion under hypnosis. He and his disciple, Muiybridge, made a report on artificial convulsions before the Philadelphia Neurological Society held at the University of Pennsylvania. The report was published in the *Journal of the Neurological Society* in 1885. The following year Dr Dercum published a paper on "The Pathology of the Nervous System" in the *Journal of the Neurological Society*.

Nervous Diseases until 1892, when he was elected to the newly created chair of Nervous and Mental Diseases in Jefferson Medical College with the title of Clinical Professor and with a seat in the faculty. In 1925 he resigned this position and immediately became Professor Emeritus.

Dr Dercum was a member of many learned societies both at home and abroad, holding membership in the Philadelphia County Medical Society, American Medical Association, Association for Research in Nervous and Mental Diseases, Historical Society of Pennsylvania, Franklin Institute, Zoological Society, Alpha Kappa Kappa, Wistar Association, Royal Medical Society of Budapest (1909), Royal Society of Medicine at London, corresponding membership in the Psychiatric and Neurological Society of Vienna (1911), and honorary membership in The Society of Physicians of Vienna (1921). He was elected a Fellow of the American College of Physicians in 1923. Dr Dercum was neurologist to the Philadelphia General Hospital from 1887 until a few years ago, when he was made consulting neurologist. He was also consulting neurologist to the Jewish Hospital, Wernersville Sanatorium and State Hospital for Criminal Insane at Fairview. He was at one time pathologist to the State Hospital for the Insane at Norristown, Pennsylvania.

As a result of assiduous literary activity throughout his long career, Dr Dercum published upward of 200 papers. As early as 1878 his scientific papers began to appear in *The American Naturalist* and in the *Proceedings of the Academy of Natural Sciences*.

They included articles on "The Sensory Organs, Suggestions With a View to Generalization" and "The Morphology of the Semi-circular Canals and the Nerve Terminations in the Lateral Sensory Apparatus of Fishes." In 1895 Dr Dercum edited a textbook of nervous diseases by American authors. His later writings included "Rest, Suggestion and Other Therapeutic Measures in Nervous and Mental Diseases," 1904, a "Clinical Manual of Mental Diseases" 1914, "Hysteria and Accident Compensation," 1916, "Biology of the Internal Secretions," 1924, and "The Physiology of the Mind," 1925. The last named work met with world-wide appreciation among neurologists and biologists and showed the author's creative originality.

In 1892 he described the *Adiposis Doloriosa*, which bears his name and is referred to by French writers as "Maladie de Dercum." It may be said that though Dr Dercum helped to give clinical observation recognition as a scientific method, he was not exclusively a clinician, but was much engrossed in scientific investigations into the causes and nature of pathological and physiological phenomena. With his friend, the late Dr Mills, he was a pioneer in the study of nervous and mental diseases.

Dr Dercum joined with Charles K. Mills, Wharton Sinkler, and others in founding the Philadelphia Neurological Society, which he served as president for a time. On December 4, 1908, Dr Dercum was formally notified that he had been elected to the *Société de Neurologie de Paris*, composed of fifty leading nerve specialists.

of the world. The only other American who has been elected to that body is Dr Charles L. Dana of New York. During the World War Dr Dercum rendered important service as a member of the Medical Advisory Board and lecturer to the Army and Navy Medical Corps.

Dr Dercum became the president of the American Philosophical Society in 1927, here he found duties commensurate with his talent, and he manifested an insatiable love for the work. About one year ago he organized the American Philosophical Society's survey of mankind's intellectual progress. It may be truly said that he infused new life into this time-honored institution.

After paying tribute to Dr Dercum's ancestors, many of whom became lawyers, judges, scholars, scientists, and physicians, and two of whom were professors in the University of Wurzburg (an institution founded in 1582 and destined to be the place where Roentgen discovered the x-ray), J. Chalmers Da Costa* says, "He should have inherited predispositions to generosity, kindness, faithfulness, hospitality, patience, charity, courage and a love for science, music and romance. I believe that he has fulfilled the promises of his ancestry."

* Address delivered at a testimonial dinner in honor of Dr Dercum's seventieth birthday, December 11, 1923.

Dr Dercum was a man of unassuming person and demeanor. He was a popular man because of the natural sweetness of his nature and his propensity to embrace every opportunity for professional, public, and social diversion. His manner was refined and pleasing, and he was uniformly cordial to his troupes of friends, both in and out of the medical profession. Indeed, the health and well-being of many of the latter depended almost as much upon his kindly attention as upon his superior skill.

Although he constantly showed himself to be a man of profound intellect and breadth of view, we shall not understand his character nor his inner life unless we conceive him as one to whom the solution of abstruse problems, particularly in psychiatry and morbid physiology of mental and nervous diseases, was an insatiable desire.

His life had been complicated, for a period of several years prior to his passing, by physical infirmities, yet his spirit had ever risen above them, its fires being fed by God-given fuel, and his genius taking up, despite interruptions, the golden threads of tasks that death alone could terminate.

In 1892 Dr Dercum married Elizabeth De Haven Comly, a member of an old Philadelphia family. Mrs Dercum and two daughters, Mrs Samuel W. Mifflin and Miss Mary De Haven Dercum, survive.

(Furnished by James M. Anders, M.D., M.A.C.P.)

Chronic Nonvalvular Cardiac Disease or Chronic Myocardial Insufficiency and Its Therapeutic Management*

By HENRY A. CHRISTIAN, M.D., F.A.C.P., *Boston, Mass*

IN an adult clinic more patients with cardiac disease without valve lesions are seen than those with valve lesions. Rheumatic fever is the largest cause of valvular disease, and this is chiefly a disease of childhood and early adult life. In children's clinics, apart from congenital heart disease, other than rheumatic valvular disease of the heart is unusual. The majority of patients with rheumatic heart disease die within a twenty year period of the inception of their heart lesion, and they have had the causative rheumatic fever in childhood. The result is a rapidly falling curve of incidence of rheumatic heart disease in hospital admissions in the years following the age of thirty.

Syphilis almost never causes any other form of heart disease than the aortic insufficiency associated with syphilitic aortitis or aneurysm. This, next to rheumatic fever, is the most frequent cause of valvular disease of the heart. The average time between causative infection with the spirochetes of syphilis and the evidences of aortic disease is between fifteen and

twenty years. Syphilitic infection is, as very aptly has been said, an incident in the bloom of youth. Certainly many syphilitic infections do begin before twenty-five. After the aortic lesion of syphilis has advanced to the stage of causing symptoms, life on the average is considerably under five years. These factors give us a rapidly falling curve of incidence of admissions to hospitals of patients with syphilitic aortic insufficiency following the forty year period of life.

After the forty year age level, hospitals have usually an increasing rather than a decreasing rate of admissions for cardiac disease, and these patients far more often than otherwise have neither the valve lesions of rheumatic heart disease nor the aortic lesions of syphilis.

As a result of examination, we know that, as a rule, these patients show the history and findings indicative of a failing circulation, symptoms and signs all too familiar for me to burden you with them, the heart with rare exceptions is enlarged, as usually can be detected by simple physical examination, but which in the obese and the emphysematous may require x-ray observation for its detection,

*Read at the Baltimore Meeting of the American College of Physicians, March 23, 1931.

heart sounds and rhythm may be normal or abnormal; murmurs may be lacking, or some sort of a systolic murmur, ordinarily loudest in the apex region, may be heard

In the rheumatic group and in the syphilitic group of patients with heart disease disturbances of valve function play an important part in causing cardiac failure. In the rheumatic group it is notable that, when symptoms of cardiac failure develop, there are in most patients well marked signs of mitral stenosis with or without auricular fibrillation. In the syphilitic group it is very striking how little cardiac enlargement there is with aortitis and aneurysm until the aortic valve becomes incompetent, and as a rule, only after these developments do we have evidences of circulatory failure. It seems reasonable to speak of both these groups as forms of chronic valvular cardiac disease.

In contrast is the striking absence of evidence of valve lesion, when one examines the heart in a patient of this past-forty group who has had neither rheumatism nor syphilis. Whether the systolic apical murmur is prominent or not seems to play little part in the degree of observed evidences of heart failure. Why not then, in contrast, speak of these as chronic non-valvular cardiac disease?

In all three of these groups the clinician, if he has had opportunity to study carefully the patient prior to the last day or two of life, can describe with very considerable accuracy what the post-mortem examination will reveal. In few realms of medicine come so few surprising revelations by the pathologist. The predicted mitral

stenosis is revealed and other valve lesions, notably aortic ones, appear or not, as anticipated in the rheumatic group, the chief failure in clinical diagnosis concerns the tricuspid valve, which may show, though rarely, an unpredicted stenotic lesion. The predicted aortic lesion with incompetent aortic cusps is as expected in the syphilitic group. In the third group, the non-valvular group, is revealed, as predicted, the cardiac enlargement without other valve lesion than the enlarged orifice resulting from dilatation of the ventricles.

The clinician and the pathologist are in accord as to the rheumatic and syphilitic etiologies. If there has been clinical doubt, and there often is, as to the etiology in the third group, the pathologist very often fails to clear the doubt. Pathological study usually confirms the ideas derived by the clinician from his examinations of the patient during life; quite rarely does it add anything of importance to those ideas.

In the first and second groups (rheumatic and syphilitic) it seems reasonably certain that a disease process of known etiology has led to organic lesion of the heart valves, and that the consequent disturbance in cardiac function has played a significant part in the progressing disease with final death of the patient.

In the third group it seems equally certain that there has been no organic lesion of the heart valves and that such failure to function on the part of the valves, as has occurred, is probably secondary to the dilatation of ventricles resulting from dilatation of aortic cusps. It would not be surprising

third group of patients has not shown any etiological factor in evidence for all of the group, nor has it revealed any pathological lesion which consistently will explain the progressing cardiac failure that has led to the patient's death. In the gross the heart muscle looks strikingly well nourished, is normal in color and appears powerful as a muscle. In some, microscopic examination will show various types of degeneration of muscle fibres and nuclei, but these obviously are of recent origin and could have no great influence in determining a cardiac failure which has increased progressively for months or even years. As a rule the muscle fibres are larger than normal. At times coronary arteries will show considerable narrowing of the lumen indicative of a lessened nutritional circulation, but just as often this is not present (none or slight in 36.9 per cent, moderate in 28.3 per cent and marked in 35.1 per cent of 228 hearts studied at autopsy) *. In some there is a diffuse fibrosis, but this definitely is unusual, and incidentally such cases differ in no wise clinically from those without diffuse fibrosis. Focal fibrosis of microscopic proportions is found more frequently (fibrosis, none or slight in 68.6 per cent, moderate in 22.5 per cent and marked in 8.9 per cent of 228 hearts studied at autopsy). There may be pathological changes in the small, terminal branches of the coronary arteries (none or slight in 48.2 per cent, moderate in 34.1 per cent and marked in 17.7 per cent of 228

hearts studied at autopsy). Often both types of sclerosis of vessels are lacking. Cellular infiltration, usually focal, occurs but is neither extensive nor frequent. In a goodly proportion of these hearts histological study shows no lesion that in its extent of distribution conceivably could explain the obvious fact that the patient has died of cardiac failure (50 out of 223 hearts), while in many others the pathological lesion scarcely seems causative of observed symptoms. A minute knowledge of the architecture of the muscle of the heart throws no light on how small focal lesions could incommode seriously the function of the heart muscle. Conceivably focal lesions might inaugurate damaging arrhythmias, but if these develop, they are relatively late in their appearance, and often these patients died without ever showing any arrhythmia.

From the clinical study of these patients it is obvious that syphilis plays no important etiological rôle, very rarely it may be a cause. Rheumatic fever certainly does not cause the disturbance. Focal infection may, at times, be a cause, but there is no satisfactory proof of this. No evidence incriminates any other infection. Definite endocrinopathies, except occasionally thyroid disturbances, are of no causative significance. In one-half to two-thirds of these patients hypertension with or without arteriosclerosis and with or without nephritis is or has been present. When it exists, it certainly would seem to be at least a contributory, if not the chief cause, and yet there are many unanswerable riddles, as we watch the progress of cardiac disability in the patient with

*These statistical studies were made at the Peter Bent Brigham Hospital by Greene FitzHugh, *New England Journal of Medicine*, 1930, ccii, 201.

hypertension Cases in every way identical with those of later life occasionally are observed at birth and in early childhood, so the aging process does not serve as a satisfactory cause

It is very striking how definite and convincing is our knowledge of what is going on, and why, in the rheumatic and syphilitic group, in contrast to its uncertainties and unconvincingness in regard to this third, or non-valvular, group

From what has been said, it is clear that, with our ignorance as to etiology in this group of non-valvular cardiac patients, methods of prevention will not be helpful in our management. The only cases with any very constant accompaniment of anything of possible etiologic significance is the hypertensive group. Assuming that in these hypertension is the cause, which may not be the case, how little does that help so long as we remain in the present state of uncertainty as to methods of controlling hypertension. We can lessen added stresses and strains but do little more than this. In those definitely of thyroid origin, the plan of treatment is directed to restoration of thyroid function to a normal level and that is not difficult. Definite foci of infection should be eliminated whenever possible; even if not etiologically important in the cardiac lesion, it is helpful to the patients' general condition to eradicate them. Indiscriminate removal of tonsils and teeth, drainage of sinuses, etc., because they might be foci of infection, is reprehensible though a frequent practice, as judged from what has happened in several cases I saw recently. The same is true of the removal of adenoids and the treatment of ear, nose and throat diseases.

avoided; many vagaries of diet are advised by food faddists which run from nothing but grapes to almost nothing but sun-kist oranges through purely vegetarian, largely meat, fat-poor, salt-poor, vitamin-rich, sugar-poor, carbohydrate-rich, and only milk and largely nut diets with the expectancy that soon some one will exploit a blubber diet which seems consistent only with life in the arctic or antarctic region, all of which dietary regimes seem to succeed in ratio to the psychological influence of the advisor and the psychopathic complex of the advisee. Excesses of weight should be reduced very gradually by food restrictions alone; one pound per week is my advised rate for the ambulatory patient.

A readjustment of mental and physical activities in accordance with circulatory disability helps much with these patients, whether they show little or much evidence of circulatory malfunction. When symptoms develop, rest with digitalis should be instituted and then a gradual return to a modified amount of activity. Increasingly I advise these patients to take continuously a daily dosage of digitalis, for most patients the equivalent in digitalis value of 0.1 gram of powdered leaves, the preparation of digitalis used seems to me to be immaterial provided it is an efficient preparation. Some patients will not tolerate 0.1 gram per day; they should have less in accord with their determined tolerance. I believe patients, who have had only the slightest evidence of cardiac inefficiency, probably from such continued digitalis ingestion, that they are well and able to

the belief that digitalis dosage might well be commenced when cardiac enlargement is detected, even though no symptoms of cardiac insufficiency have yet appeared. The belief that digitalis is useful only in the presence of auricular fibrillation seems still to persist, though there is much very striking clinical evidence against it, especially strong for this particular group of patients.

Terminology for this group of patients is confused. Chronic non-valvular cardiac disease seems to me a good

term. Chronic myocardial insufficiency is not unsatisfactory. Chronic myocarditis, too, would be satisfactory, if one will admit that it does not connote inflammation of the myocardium, but long usage renders that difficult. Any of these terms can be modified by adding an adjective descriptive of the cause, when known, such as hypertensive, hyperthyroid, etc. On the basis of present knowledge I prefer chronic non-valvular cardiac disease, if one speaks of the other groups as cases of chronic valvular cardiac disease.

Circulatory Adjustments in Heart Disease: A Concept of Circulatory Failure*†

By SOMA WEISS, M D , F A C P , *Boston, Mass*

IN TENSIVE clinical and experimental studies of the heart and circulation during the past quarter century have shed considerable light on problems of the cardiovascular system. The accumulated facts, however, are of less aid in understanding the clinical picture of cardiac and circulatory diseases than one would expect. Discoveries with the galvanometer have revealed in detail the mechanism of various disturbances in the conduction of nerve impulses and in the excitability of the myocardium. Correlations between the clinical behavior of the patient and the electrocardiographic findings have made the clinical diagnosis of cardiac pathology more accurate than before, but, on the other hand, have disclosed little concerning the efficiency of the heart. The electrocardiogram is not a direct measure of the state of the circulation. A patient with auricular fibrillation, diagnosed as "pulsus irregularis perpetuus" during the Spanish-American War,

is still at hard daily physical work. Another patient, showing a similar electrocardiogram, is dying with congestive failure of the circulation. Recently we observed a patient who maintained a fairly efficient circulation with ventricular tachycardia for thirty-five days and then reverted to normal sinus rhythm.

A majority of the symptoms and signs of the patient with cardiovascular disease depend rather on the state of the circulation than on the heart. Knowledge of the conditions underlying the clinical picture of circulatory failure is still exceedingly meager. We have no satisfactory explanation of why one patient develops an early hydrothorax, while another dies of massive peripheral edema with no trace of fluid in the pleural cavity. The interpretations of the correlation of the clinical manifestations of heart disease are but empirical and often confusing.

It is not surprising that progress in this branch of medicine has lagged behind, for the factors which determine the clinical picture of circulatory failure are numerous and variable. If many be present, the clinical picture becomes more complex and the diagnosis

*From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard) of the Boston City Hospital, and the Department of Medicine, Harvard Medical School, Boston, Mass.

†Presented at the Education Meeting of the American College of Physicians, March 1935.

unfavorable changes Furthermore, not only are there various changes and adjustments present in different types of heart disease; but in different stages of the same type of heart disease, new factors, or different combinations of factors, may be responsible for the same clinical manifestation To understand circulatory failure, a study of the patient with a correlation of the combined chemical, physiological and morphological factors, instead of a separate analysis of single aspects, is especially important Chemistry, physiology and anatomy are dependent on each other; they may be separated successfully in theory but are combined with equal importance in practice

From the available evidence it is thus difficult to construct as yet an accurate and detailed picture of the sequence of events in the progress of circulatory failure The difficulty is great not only because numerous gaps exist at the most crucial points of the problem, but also because results of the investigations are often contradictory even concerning the most diligently studied aspects of the circulation A concept, therefore, which attempts to correlate the clinical picture with the functional and structural changes of circulatory failure can be at its best, but incomplete Nevertheless, it is desirable from time to time to assemble the scattered blocks of knowledge and then inspect them from a distance in the hope that they may assume the outlines of a real structure, even though broken by spaces Such a concept, despite its incompleteness, helps in the estimation of the clinical condition of the patient ^{medical} and in the

proper application of therapeutic measures

In the course of this limited discussion it is impossible to enter into an intricate interpretation of the individual symptoms and signs of circulatory failure The following presentation will therefore be limited to those alterations of circulatory function which bear closely on the clinical manifestations of circulatory failure Factors referable to the heart will not be discussed Correlations of the circulatory functions are presented partly from clinical observations and investigations conducted in the Boston City Hospital during the past five years, and partly from the results obtained by other investigators Occasionally, when reliable observations on man are not available, analogous experimental observations on animals are used It is hoped that clinical studies in progress will yield more direct proof on these points Controversial discussions will be omitted

I. HEART DISEASE AND CIRCULATORY FAILURE

Whenever the circulation fails to accomplish its task of efficiently supplying the tissues with nourishment and promptly eliminating the waste products of cell metabolism during the normal activities of life, we speak of circulatory failure Normal circulatory efficiency, like so many other biological functions, is a broad average since considerable variation exists among healthy individuals Heart disease may coexist with a circulation normal in every respect for years. Often, however, long before actual impairment of the efficiency of the body

occurs, alterations and adjustments take place in various parts of the circulation. Thus, for example, a patient may perform normal amounts of daily work, but accomplish this with a higher expenditure of cardiac energy, an increased ventilation of the lungs, a higher arterial blood pressure, and an increased utilization of oxygen and exchange of other substances between the capillary blood and tissue cells. These adjustments make it possible for the patient to perform vital functions which otherwise could not be carried on.

In the presence of heart disease the nature of the readjustment of the circulation depends to a certain degree quantitatively and qualitatively on the localization and etiology of the cardiac lesions. However, failure of the circulation may be independent of heart disease. For this reason, it is erroneous to speak of heart disease and circulatory failure interchangeably. Circulatory failure often results from primary derangement of the vasomotor system. Such is the case in the progressive vasomotor collapse (shock) which follows surgical operations and other types of trauma, in certain diseases of the nervous system, infectious diseases and toxemias. The clinical picture of vasomotor collapse is quite distinct from that of congestive heart disease. The patient is pale; dyspnea may be present but without orthopnea; the veins are collapsed instead of being dilated; the circulating blood volume is early reduced, due to stagnation of blood in the peripheral minute vessels. Correspondingly, there is a decrease in the minute and stroke volume output of the heart;

and as a result of this, the venous and arterial blood pressures fall below normal although the mean velocity of blood flow may be unaltered^{1,2}. There is a depletion of the blood content of the large vessels and chambers of the heart, and an overfilling of the peripheral minute vessels due to purposeless relaxation of the arterioles and perhaps other minute vessels. The heart expels with ease whatever blood reaches its chambers.

Vasomotor collapse does not always exist in this pure form, as the chemical factors which cause the collapse may also depress the heart function. This may be the case in lobar pneumonia. In such instances the clinical picture and the type of circulatory failure depend on a combination of vasomotor collapse and heart failure.

Certain investigations have suggested that primary changes in the peripheral circulation are also responsible for the failure of the circulation in heart disease. Thus it has been claimed that primary disturbances in the lactic acid metabolism cause important changes in the peripheral vascular system and precipitate the sequence of events that results in circulatory failure. A recent investigation in the Boston City Hospital fails to support this claim. No primary disturbances of the lactic acid formation before the appearance of an inadequate blood flow could be discovered. All the evidence obtained by us thus far supports the logical concept suggested by clinical manifestations and post mortem findings, that local disturbances of the heart are primarily responsible for the circulatory changes.

The clinical picture of circulatory failure varies, depending on the etiology of the heart disease and the seat of the lesions. Because the cardiac lesions are rarely in pure form and the size and rate of their development are usually unknown factors, the clinical picture of failure varies considerably even in a group of patients with similar morbid changes in the heart, so far as can be judged from clinical observations.

In this presentation, for the sake of simplicity, the circulatory adaptations will be correlated, as a rule, with the normal basal metabolism at rest. In reality the circulatory efficiency can be considered as an index between efficient capillary blood supply and tissue metabolism. This index may be disturbed both by abnormal changes of the circulation or by increase in metabolism. For obvious reasons, in the presence of markedly increased metabolism a relatively slight circulatory failure leads to severe clinical disturbances. Clinical symptoms and signs are often the expressions of an altered balance rather than absolute deviations from normal. In addition to changes in the heart, numerous extracardiac factors may influence the circulation and thus the clinical picture. Of these factors, fever of bacterial or non-bacterial origin; altered hemoglobin and protein content of the blood, pulmonary pathology, especially emphysema and bronchitis; and internal secretory disturbances are most important. The way in which these factors influence, at times fundamentally, the circulation cannot be discussed here.

II. EARLY STAGES OF CIRCULATORY FAILURE

"Congestive heart failure" with dyspnea and orthopnea at rest, râles over the base of the lungs, hydrothorax, enlarged liver, ascites, and dependent edema is usually the end picture of chronic disease of years' duration. For a long period before this stage of circulatory failure is reached the patient is comfortable at rest and develops circulatory embarrassment only after exertion. At this stage, the patient with heart disease differs apparently from normal subjects only in the degree of muscular activity that brings on dyspnea and weakness. This early stage is the longest period in the natural course of heart disease, and it is in this stage that intelligent preventive measures will ameliorate and prolong the life of the patient. Unfortunately, this period of circulatory failure is most incompletely understood.

At the onset of circulatory failure the symptoms and signs are referable almost entirely to local disturbances in cardiac function. The main symptom referable to the circulation is dyspnea; and it is the mechanism underlying this dyspnea that is the center of the problem. If one examines the state of the peripheral circulation at this stage one finds that the arterial, capillary and venous blood pressures are unaltered. The cardiac output per minute may be normal or slightly reduced^{4,5}. The velocity of blood flow as observed in the capillaries of the finger nail bed⁶ as well as in the large veins of the forearm⁷ is frequently normal. Hence the velocity in the

arteries must also be unaltered. Similarly, the arterio-venous oxygen differences of the arms and legs and the lactic acid content of the arterial and venous blood are normal⁸. In other words, all the studies with available methods indicate that the blood supply of the organs is adequate and normal at rest. Even more significant is the fact that if a patient performs a walking exercise sufficient to induce dyspnea, and the arterio-venous oxygen differences are studied by repeated punctures of the femoral and cubital veins, not only the volume difference of oxygen but the rate of the return of the oxygen difference to normal is the same in cardiac patients with dyspnea as in the normal subject who experiences no difficulty in performing the same exercise⁹. It is also significant that the curve of the lactic acid content of the blood in the femoral vein after exercise shows the same rise and return to normal as that of normal individuals. There is no difference in the lactic acid overflow into the blood from exercised muscle in the dyspneic cardiac patient and in the normal subject who experiences no dyspnea³. These recent observations indicate that in the early stages of circulatory failure, when the patient becomes dyspneic after mild exercise, the peripheral supply of blood to the tissues may still be adequate and the lactic acid formation in the exercising muscle not disturbed.

What, then, are the factors which show deviation from normal at this stage? One does find early a reduction of the vital capacity of the lungs^{10,11}. Simultaneously, or somewhat later, the blood flow through the lungs is re-

tarded. If the total lung volume, as well as the interrelation between various portions of the respiratory space are measured, one finds that the total lung volume is normal or may even be increased^{10,11}. The residual air, instead of being decreased as one would expect from the diminished vital capacity, may be increased both relatively and absolutely, often at the expense of the reserve air, which decreases. A disproportion therefore develops between the residual air and the reserve air¹¹. Unfortunately, no observations on the pressure relations in the pulmonary circuit in man are available.

Is it possible to correlate these physiological observations with the structural changes and the behavior of the patient? It seems significant that all the abnormal findings observed in the early stages of circulatory failure bear on the pulmonary circulation and on the structural and physiological alterations of the respiratory surface while, on the other hand, the larger circulation shows no morbid changes. This obviously justifies two conclusions of great significance. (a) *that in early stages of circulatory failure changes occur in the pulmonary circulation;* and (b) *that changes in the pulmonary circulation may be independent of the larger circulation*.

In rheumatic, syphilitic, hypertensive and arteriosclerotic heart disease it is in the pulmonary venous system that the first effect of the heart disease manifests itself*. The back pressure

*Triumph's disease is that other vascular disease in rheumatic heart disease, and coronary sclerosis may have the blood supply of the right ventricle alone as its main seat.

effect in cases of mitral disease and in cases of failure of the left ventricle is obvious. Its occurrence was claimed, long before the application of physiological concepts to clinical medicine, by morphologists of the 17th century. But the significance of this back pressure effect has not been examined in detail. If the left ventricle is not normally efficient and a certain amount of blood accumulates in the pulmonary vein, one or a combination of two possibilities may occur. (a) there being no essential alteration in the cross-sectional area of the vascular portion which offers the resistance to the right ventricle, *the increase in the pulmonary venous pressure will result in a proportional increase in the pulmonary capillary pressure, and later, in the pulmonary arterial pressure,* (b) *a considerable increase in the cross section and volume of the vascular bed of the pulmonary circuit may result without necessitating much alteration in pulmonary arterial pressure.* Teleological and experimental evidence strongly supports the presence of the second factor in early stages of circulatory failure.

It is now established that reserve capillaries exist in almost all the organs so far investigated. It would be most unusual if the lungs, the specific function of which depends entirely on capillary activity, did not possess such reserve capillaries. Their existence in the lungs has been suspected ever since the work of Cohnheim and Litten¹² in 1876. In rabbits, reserve capillaries which open during physiological activity were graphically demonstrated by Toyama¹³ in 1925. In cats, the opening of new capillaries was ob-

served by Wearn, Barr and German¹⁴. Hall¹⁵ denies the appearance of new capillaries in the lungs with unchanged activity. He did not study the problem of reserve capillaries in the presence of various states of the circulation. Therefore the existence of reserve capillaries in the lungs can be considered as established.

Increase in the venous pressure is one of the most effective means by which reserve capillaries can be opened in the larger circuit. In human beings this can be demonstrated with surface capillaries of the skin¹⁶. Whether the opening of the capillaries induced by increased venous pressure is a passive phenomenon depending on the widening of the arterioles, or an active process, or whether chemical, physical or local reflex factors regulate their opening does not bear on the problem discussed here. The importance of the widening of the arterioles and the opening of new capillaries to the local maintenance and regulation of adequate peripheral blood flow in the presence of congestion in the peripheral veins has been repeatedly demonstrated and emphasized in recent years. We believe that *in progressive heart failure the pulmonary arterioles widen and a reserve capillary bed opens in the lungs, and that the mechanism of this process is governed by the same physiological laws as have been demonstrated in the peripheral circulation.* This concept is not only supported by a number of observations, but it explains several apparently contradictory and isolated observations previously not understood. Wearn and his associates¹⁷ observed that new capillaries appear regularly when back

pressure is induced in the pulmonary vein by pressure over the aorta. Such pressure is more efficacious in opening the capillaries than increasing the blood flow and the pulmonary arterial pressure with adrenalin. In rheumatic heart disease and arterial hypertension a retardation of the maximal velocity of the blood flow through the lungs may occur with a normal or only slightly reduced cardiac output. In the later stages of circulatory failure again the degree of retardation of the blood velocity in the lungs is more marked than the reduction of the volume blood flow, as judged from the oxygen utilization in the upper and lower extremities³. This apparent discrepancy between the velocity and volume flow can be explained only by an increase in the cross-sectional area of the capillary bed. Such an increase may occur (a) through the stretching of previously opened capillaries, or (b) through the opening of new capillaries. The first possibility is not supported by experiments, and furthermore would be a purposeless and harmful mechanism. It would result in an early and marked increase in the pulmonary and capillary arterial pressure, which would soon damage the right ventricle and lead to pulmonary edema. Instead of one row, two rows of red corpuscles would pass through the capillaries, and this in turn would make the exchange of blood gases incomplete. As early as 1876, Lichtheim¹⁸ showed that considerable occlusion of the left pulmonary artery fails to induce any appreciable alteration in the pressure of the right pulmonary artery or of the aorta. Lichtheim concluded, therefore, that the amount of blood flow-

ing through the right lung was unaltered. He attempted to explain his observations on the basis of a compensatory increase in the diameter of the pulmonary artery.

Increase in the cross-sectional area may occur without any appreciable elevation in the resistance of the arteriolar and capillary beds of the lungs. All of these observations, therefore, indicate directly or indirectly that the increased cross-section develops through a widening of the arterioles and an opening of the reserve capillaries. A progressive increase of the capillaries makes it possible to maintain a normal or approximately normal volume of blood flow through the lungs per unit of time without much added burden to the right side of the heart. It is probably this mechanism which makes it possible for the patient with heart disease to live fairly comfortably for many years.

The opening up of numerous new capillaries along the alveolar surface and the moderately increased capillary pressure must have an important effect on the shape and consistency of the alveoli, which explains the stiffening observed experimentally by von Basch and his pupils some fifty years ago¹⁹. This dilatation and stiffening of the alveoli increases the residual air, relatively or absolutely, depending on whether or not the residual air increases at the expense of the reserve air of the lung. These changes in turn are responsible for the early decrease in the vital capacity. The reduction in the vital capacity, therefore, is not dependent on the volume of the blood on the chest, but rather on the development of a firm

emphysema of the alveoli induced by the opening of new capillaries under normal or higher than normal tension

The increased blood volume in the lungs does not decrease the total air space but rather causes the diaphragm and bony thorax to assume a slightly inspiratory position, thus allowing space for the increased total blood volume

If one accepts this theory of the circulatory and respiratory mechanisms one can then clearly understand that the development of dyspnea in heart disease is primarily due to the active rôle of pulmonary arterioles and reserve capillaries and to a functional emphysema. It is also possible that loss of elasticity of the alveolar wall *per se* makes expiration difficult and thus adds to the subjective sensation of dyspnea. In the finer analysis of the mechanism of dyspnea, reflexes between the lungs and the respiratory center activated by the changes just described play an important rôle. Numerous animal experiments reported in the literature also support the contention that *dyspnea in the early stage of circulatory failure is produced through nervous communications between the pulmonary system and the medulla and not by local chemical changes within the respiratory center*. Finally, the concept proposed not only brings into harmony the apparent contradictory findings referable to the pulmonary circulation but also offers a rational explanation for the fact, repeatedly demonstrated experimentally on animals since Lichtheim's original studies¹⁸, that the peripheral circulation may be normal despite changes in the pulmonary circulation

and in the alveoli and pulmonary reflexes

III. LATER STAGES OF CIRCULATORY FAILURE

In contrast to the early stages of circulatory failure, the later stages exhibit numerous *clinical manifestations*. With the progress of the dysfunction of the left ventricle, symptoms and signs of "congestive failure" gradually appear with cyanosis, râles over the base of the lungs, hydrothorax, dyspnea after slight or no exertion, orthopnea, increasing engorgement of the veins of the larger circuit, enlarged liver, ascites, peripheral edema and other well recognized clinical manifestations. Considerable variations occur clinically both in the appearance and the combination of these manifestations.

If one computes the various aspects of the circulation that have been *measured quantitatively in man*, one frequently finds the following sequence of changes. The vital capacity and the velocity of the blood flow become increasingly diminished²⁰. These two measurements may deviate 100 per cent or more from their normal values. With these marked changes comes a tendency to a decreased cardiac output of blood. The decrease in the blood volume flow through the lungs is normally not as marked as the degree of slowing of blood flow. Simultaneously, the peripheral venous pressure rises steadily above normal values. Greater and greater amounts of oxygen are utilized in the capillary blood, which, while the body is in the upright position, may reach oxygen values of as high as 16 to 17 volumes

per cent after slight exertion⁸. If the congestion in the lungs is marked, difficulty in the aeration of the blood reduces the oxygen saturation of the arterial blood. Only when the peripheral adaptations of the larger circulation have been exhausted do there develop, rather late in the natural course of circulatory failure, physicochemical disturbances of the blood, such as an increased lactic acid content, an altered buffer capacity, and changes in the hydrogen ion concentration. When these changes appear even at rest, the tissues of the entire body are severely affected in the performance of their necessary functions. Disturbances in the local or peripheral vasomotor reflexes are then an expression of extreme failure of the circulation.

The concept outlined in the previous chapter may be expanded even further, on the basis of the clinical observations and the quantitative measurements of the circulation during moderate or severe failure described above, in an attempt to obtain a more complete insight into the sequence of events. As the cardiac dysfunction progresses, the pressure in the pulmonary vein must rise further. This produces further compensatory dilatation of the pulmonary arteriolar system and hence an increase in the number of open capillaries. At the same time, in order that an adequate amount of blood should flow through the lungs, the pressure in the capillary bed must increase to correspond to the elevated pressure in the pulmonary vein. Considerable increase in the capillary pressure may occur without necessitating an increase of pressure in the pulmonary artery, since the widening of the

arterioles means that a relatively high arteriolar pressure is exerted increasingly on the capillaries, thus establishing an optimal or almost optimal pressure gradient between the capillaries and veins. In the previous study of the peripheral circulation²¹ it was shown that by inducing a relaxation of the arterioles the capillary pressure might rise to such high values as from 46 to 65 mm. in normal subjects, and from 60 to 150 mm. in patients with hypertension. By analogy, it is possible that the pulmonary capillary pressure might rise to about 20 mm. of mercury through arteriolar regulation. Only when the compensatory arteriolar pressure is exhausted will the pulmonary arterial pressure have to rise to correspond to a further increase in the venous pressure. With these progressive changes in the pulmonary circuit, there must be an increasing stiffening of the alveoli and an increase in the total volume of blood in the lungs. This is obviously present, as indicated by post mortem observation. The diaphragm tends to fall, and thus, partly for mechanical, partly for nervous reasons, the rapid, shallow respiration of the cardiac patient becomes necessary. Obviously, changes in the lung function due to pathologic alterations in the pulmonary circulation are, disregarding chemical disturbances of the blood, the primary factors in the respiratory difficulty. The dyspnea of the cardiac patient at this stage is still a local pulmonary problem. (The reflex interrelation between the changes in the lungs and the respiratory center cannot be entered into here). Thus the cardiac patient with severe primary disturbances in the pulmonary

circulation behaves to a certain extent not dissimilarly to the patient with acute emphysema. This concept is further supported by the occurrence in the cardiac patient of a distinctive type of respiration, the inspiratory position of the thorax, and the low diaphragm which often retracts the lower costal margins during inspiration. It explains also why cardiac dyspnea is often associated with expiratory difficulties in contrast to the dyspnea which develops in patients without heart disease after central stimulation. In patients with emphysema the changes in the lungs are independent of the circulation; in cardiac patients they are secondary to it.

There is another important factor in circulatory failure. The pressure in the pulmonary vein, both in normal subjects and in patients with circulatory failure, depends on gravity. Just as in the larger circuit, gravity increases the pulmonary venous pressure progressively below the level of the left auricle. As long as the circulation is normal this factor plays no obvious rôle. However, if, as in advanced failure, the pressure in the left auricle increases considerably, the situation becomes quite different. Under such conditions the pressure over the lower portion of the pulmonary vein must be considerably higher than over the upper portion of the lungs. Indeed, over the base it may become so high that neither the arteriolar nor the arterial pulmonary pressure can raise the capillary pressure sufficiently to insure an adequate capillary blood flow. Considerable slowing of the blood flow in the base of the lungs must occur at this stage, while the flow over

the upper portion of the lung must be more rapid. Finally, a stagnation of the blood flow results in "sedimentation of the blood" in the hypostatic portion of the lung leading finally to transudation of the serum. This "sedimentation of the blood" can be demonstrated by simple experiments in rabbits which are susceptible to postural changes from horizontal to upright position. It is this mechanism that produces clinical signs of pulmonary congestion.

Obviously, with the approach of pulmonary congestion, the vital capacity is diminished not only by the factors discussed in the previous section, but by the encroachment of stagnant blood on the alveolar spaces. This explains why measurements of the lung volume in this stage show a diminution of the total air spaces as well as of the residual air of the lungs¹⁰.

The orthopnea in cardiac patients with clinical evidence of pulmonary engorgement, prolonged velocity, lowered vital capacity but no elevation in the venous pressure, is due partly to the same causes as emphysema or asthma, partly to the fact that upright posture may elevate a considerable portion of the lungs and make possible the maintenance of the pulmonary blood flow with less strain on the right side of the heart²².

The consideration outlined clearly suggests the possibility that *a normal or decreased amount of blood may flow through the lungs under entirely different pressure relations within the pulmonary circuit. Thus the same minute volume of blood flow may represent different burdens for the right ventricle in different states of the cir-*

culation This explains also the hitherto paradoxical observations that digitalis occasionally may benefit the patient without materially altering the cardiac output or velocity of pulmonary blood flow^{4,23}. *The measurement of the amount of blood flow, without knowledge of the pressure in the pulmonary circuit, gives no indication of the energy expended by the right ventricle to maintain this blood flow.* We are dealing here with a mechanism somewhat similar to that of arterial hypertension of the larger circuit⁵.

With an embarrassment of the right ventricle which, depending on numerous factors, may occur at various stages of the pulmonary circulatory disturbance, the peripheral venous pressure increases considerably. There is also a definite slowing of the venous blood flow. The velocity of the arterial blood is not sufficiently known at present. However, certain studies indicate that it is slower in congestive failure²⁴. Considering, however, that as far as can be ascertained, the diameters of the large arteries do not show gross alterations in congestive failure, that the arterial blood pressure frequently remains unaltered; and that the blood volume and flow may be normal or lowered, one may justifiably conclude that the *slowing of the blood flow in the arterial system, if present, must be less than in the venous system.* Furthermore, as has been observed in a group of patients with advanced circulatory failure and venous congestion, the volume flow of blood to the legs may be normal and the arterial blood pressure unaltered. Thus the volume and ve-

locity of the blood flow through the arterial system may be normal even when there is a considerable slowing in the venous system. This is substantiated by the fact that in patients whose arterial blood pressure was normal and whose venous pressure was considerably elevated up to the time of impending collapse of the circulation, post mortem examination shows a normal diameter of the aorta and large arteries but a marked increase in the diameters of the vena cava and other large veins. If during life a compensatory constriction of the arteries occurs, a rational possibility neither proved at present nor demonstrable by post mortem observations, such a mechanism would tend to maintain a normal velocity in the arterial system. The aorta could not play an active rôle in such a mechanism as it is incapable of active constriction or dilatation²⁵. These considerations again bring out the following perhaps obvious, but nevertheless not fully appreciated facts concerning circulatory failure. (a) *although in a given time the total amount of blood flowing through a cross-sectional area of the larger arteries must be the same as that in the large veins; nevertheless, because of the independence and variety of the changes in the diameter of the cross-sectional areas in the venous and arterial systems, an abnormal deviation of the velocity of blood in the venous system may develop quite independently of any changes in the velocity of the arterial system,* (b) *changes in pressure in the arterial and venous systems and velocity are to a considerable extent independent.* These concepts are a rational explanation of

the fact that the arterial pressure, regardless of the degree of circulatory failure, may be normal, lowered, or slightly elevated even at a time when venous engorgement exists

Increased venous pressure has an important effect on the capillary circulation which performs the basic tasks of the blood and circulation both in the lungs and in the periphery. As described previously, it has been repeatedly demonstrated in animals and also in man that a sensitive regulation makes it possible that an optimal capillary circulation is maintained even in the presence of a gradually increasing venous pressure. Widening of the arterioles, through nervous reflexes, chemical regulation, or elevation of the arterial blood pressure, plays a dominant rôle in maintaining this regulation. The opening of new capillaries and increased oxygen utilization are then perhaps further consequences of, rather than independent processes in, the changes that follow venous engorgement.

In the presence of severe venous engorgement the capillary pressure inevitably rises. *Thus the capillaries of the patient with congestive heart failure are always under abnormal pressure wherever the venous pressure is elevated. The velocity of the capillary blood flow is independent of the capillary pressure, and is to a certain extent determined by the functional capacity of the left ventricle.* Thus, for example, we have evidence that in hemiplegia the capillary pressure over the paralyzed side is often increased, both relatively and absolutely, with the presence of increased velocity of blood flow⁶². *The balance between the*

functional capacity of the left ventricle, and the velocity of the capillary blood flow on the one hand, and the degree of elevation of the capillary pressure on the other, has a fundamental relationship to cellular nutrition and function. High capillary pressure, and a blood flow low in volume and velocity, such as occur in numerous instances of congestive failure, are a combination seriously damaging to tissue function. It produces not only a "passive congestion" and an edema *per se*—but as a result of disturbances of the internal respiration between the capillary blood and tissue cells, specific chemical substances, depending on the organs involved, appear in abnormal quantity in the blood stream. In these disturbances of tissue functions ischemia and anoxemia play important rôles, but they seldom occur without the presence of high capillary pressure and slow blood flow. Some substances, like histamine, will further specifically damage the capillary system. Others, like lactic and other acids, will increase the dyspnea through central stimulation. At this stage central chemical stimulation, in addition to the pulmonary reflexes, plays an important rôle in the production of cardiac dyspnea. Circulatory damage to the liver will completely upset the water metabolism. Circulatory changes in the kidney and other organs will break the sensitive and vital mechanism that maintains a constant acid-base equilibrium in the blood and tissues. Thus that stage of circulatory failure is now reached when the localized disease of the heart becomes a grave and extensive disease of metabolism, leading to death.

IV. CERTAIN APPLICATIONS OF THE CONCEPT PRESENTED

It has been suggested in this discussion that the simultaneous consideration of the pressure relationships in the veins, capillaries, arterioles and arteries, of the volume and velocity of blood flow, and of the permeability of the capillary system in the pulmonary and peripheral circulation together with the oxygen carrying capacity of the blood and the oxygen requirement of tissue, clarifies considerably our understanding of the clinical manifestations of heart failure. The relationship between these and other bodily functions during progressive heart disease has been computed from a series of observations and studies on a large group of patients with heart disease. Yet such a schematic presentation would carry false implications unless certain reservations were made.

Obviously not every patient with heart disease will proceed through all the stages described. Observations of the types and causes of death in cardiac patients reveal that a relatively small group of patients die in the last stage of the progressive congestive failure. Death frequently occurs abruptly at earlier stages because of precipitated arrhythmias of the heart, coronary occlusions, embolism or other vascular accidents, and uremia. Pulmonary congestion predisposes to bronchopneumonia and the added burden of this or other infections, for obvious reasons, is responsible for the death of another large percentage of cases. There is, finally, a group of patients in whom apparently none of the above factors are active. These patients, although the circulatory func-

tions are still fairly well sustained, exhibit sudden changes in clinical appearance and die within a few hours. A number develop a rapid pulse, low blood pressure, cold skin, dyspnea, abnormal vasomotor reflexes and die with clinical evidence of peripheral vasomotor collapse and shock. One wonders whether in such instances the long persisting dyspnea, cardiac pain, rapid heart rate and other factors subject the central nervous system to an abnormal bombardment, thus causing death through a failure of the vasomotor and perhaps other nerve centers rather than through extreme congestive circulatory failure.

In applying this concept of circulatory failure to different types of heart disease the *time element* and the *nature of the cardiac lesion* should always be considered. A few examples of this will be briefly outlined, as these factors with the physiological principles presented will clarify the variations in the clinical course of circulatory failure in different types of heart disease. In the *mitral stenosis* of rheumatic fever the disturbance in the pulmonary circuit develops rather slowly and hence the right ventricle is considerably embarrassed when the pulmonary engorgement reaches a severe level. The simultaneous failure of the right side of the heart at this stage reduces the pulmonary pressure. There is thus a fairly definite relation between the pulmonary and peripheral congestion. In *arterial hypertension and aortic insufficiency*, on the other hand, an appreciable rise of pressure in the pulmonary vein occurs relatively late and only when there is a failure of the left ventricle. Hence

the engorgement and disturbance in the pulmonary circuit develop rapidly and at a period when the right ventricle has still a normal functional capacity. For this reason, evidence of pulmonary circulatory embarrassment with congestion, dyspnea, orthopnea and right hydrothorax are observed frequently in these patients in conjunction with fairly normal peripheral circulation. The same consideration bears closely on the occurrence of paroxysmal dyspnea with or without bronchial asthma early in this type of circulatory failure; and also explains a frequent clinical observation that with the onset of failure of the peripheral circulation these paroxysms frequently disappear. The onset of failure of the right side of the heart prevents the maximal elevation of the capillary pressure in the lungs and shunts a part of the blood into the periphery. As a result, the disproportion between the pressure in the pulmonary and peripheral circulation decreases and, for this reason, the patient improves subjectively and the dyspnea and orthopnea often become less. Also the state of the circulation is less favorable to the development of asthma and of right hydrothorax.

Not infrequently with the development of dependent edema and ascites, the hydrothorax disappears. Recently we observed, in the few instances studied, that with the onset of edema and ascites the velocity of blood flow through the pulmonary circuit increased and subjectively the patient felt better²³.

In accordance with the concept, it is obvious why a patient with pure *tricuspid insufficiency* may be less in-

capacitated with a higher venous pressure and more cyanosis than a patient with circulatory failure due to syphilitic aortic insufficiency. The pulmonary embarrassment in this condition is less, and although the venous pressure is high, the volume flow and velocity may be fairly well maintained, due to the fact that the left ventricle is efficient.

In the circulatory failure associated with preponderant embarrassment of the right or left ventricle, such as occurs in rheumatic, syphilitic and hypertensive heart disease, the disturbances in the circulation, for reasons discussed above, occur more in one portion of the vascular bed than in others. In the myocardial failure which accompanies *aging* there appears clinically a fairly *parallel failure* of both ventricles and thus the disturbances in the pulmonary and peripheral circulation tend also to be parallel. Since aging processes impair the reserve functions of all organs, including the brain, the efforts of senile patients are not apt to be out of proportion to the functional capacity of the heart. These are probably the chief reasons why a number of old people exhibit a considerable restriction in functional capacity without a clinical picture of marked congestive failure. Thus "dry failure" is not necessarily the expression of a better circulatory efficiency than congestive failure. Naturally, if through aging processes the blood supply of one ventricle, especially of the left, is more impaired than the other, the development of one or the other type of congestive circulatory failure occurs.

The prognostic significance of individual symptoms and signs of circulatory failure can be estimated only if the underlying mechanism is understood. Dyspnea, hydrothorax, cyanosis, edema and other manifestations may result from various combinations of factors and therefore the same symptom in different patients or in the same patient at different times may have a varying significance. Another reason why a single clinical manifestation has, as mentioned before, no standard significance, is that certain extracardiac factors may play a fundamental rôle in the development of the same sign. For example, the occurrence of infection during early circulatory failure may damage the peripheral arterioles, thus leading to increased capillary pressure without venous engorgement or edema. In another instance, loss of protein due to kidney damage may hasten the development of edema in a stage of circulatory failure which by itself would not produce this sign. Right hydrothorax may be the result of pulmonary engorgement, or in other instances to local pressure on the azygos vein due to aneurysm of the aorta or dilatation of the auricles or ventricles.

Numerous other specific applications of the concept may be given; but the purpose of this presentation is not a detailed analysis of the various phases, symptoms and signs of circulatory failure, but rather the interpretation of those essential clinical and laboratory observations which are of practical importance to the physician in interpreting rationally the history and physical signs of the patient. The proper use of the principles empha-

sized should make diagnosis, prognosis and therapy more accurate. It is hoped that investigations in progress will yield additional facts to fill out the portion of this discussion at present unsupported by observations on patients.

SUMMARY AND CONCLUSIONS

1. On the basis of a series of investigations and clinical observations on patients, a concept of progressive circulatory failure has been formulated. This concept brings into harmony hitherto uncoordinated and apparently contradictory observations. It offers a rational and more exact interpretation of the clinical manifestations of circulatory failure associated with cardiovascular diseases.

2. The interrelations between pressure, volume and velocity of blood in various portions of the pulmonary and larger circulation and in turn their relations to other bodily changes in various stages of circulatory failure are discussed. The regulatory adjustments are so complex that simultaneous measurements of several aspects of the circulation are essential to an accurate analysis of clinical symptoms and signs.

3. In the early stages of circulatory failure marked alterations occur in the pulmonary circulation, while the larger circulation is normally maintained. The elevated pulmonary venous pressure is primarily responsible for the disturbed pulmonary circulation. Recent advances in the physiology of the pulmonary circulation substantiate the concept of the beneficial regulatory functions of the pulmonary

arteriolar and capillary system. The same volume or velocity of blood flow through the lungs in various stages of failure may represent different burdens for the right ventricle and the ventilative mechanism of the lungs, and hence may be associated with varied clinical manifestations.

4 The dyspnea of early circulatory failure depends to a large extent on the altered function of the alveoli of the lung, which is secondary to changes and regulatory adjustments in the lesser circulation. These pulmonary changes set up reflexes be-

tween the lungs and the respiratory center. Chemical stimulation of the respiratory center is present only in the late stage of congestive failure of the larger circulation.

5 In failure of the larger circulation changes in pressure and velocity of blood flow may develop independently in the arteries and veins.

6 The combination of elevated capillary pressure with decreased velocity and volume flow are the chief factors responsible for damage of cell nutrition in the later stages of circulatory failure.

BIBLIOGRAPHY

- ¹EPPINGER, H, and SCHÜRMEYER, A. Ueber Kollaps und analoge Zustände, *Klin Wchnschr*, 1928, vii, 777.
- ²EPPINGER, H. Ueber den postoperativen Schock, *Wien klin. Wchnschr*, 1931, xlv, 65.
- ³WEISS, SOMA, and ELLIS, L. B. Heart disease and peripheral circulation, *Jr Clin Invest* (in press).
- ⁴WEISS, SOMA, and ELLIS, L. B. Circulatory measurements in patients with rheumatic heart disease before and after the administration of digitalis, *Jr Clin Invest*, 1930, vii, 435.
- ⁵WEISS, SOMA, and ELLIS, L. B. The quantitative aspects and dynamics of the circulatory mechanism in arterial hypertension, *Am Heart Jr*, 1930, 4, 448.
- ⁶WEISS, SOMA. Unpublished observations.
- ⁷BLUMGART, H. L., and WEISS, SOMA. Clinical studies on the velocity of blood flow, IX. The pulmonary circulation time, the velocity of venous blood flow to the heart, and related aspects of the circulation in patients with cardiovascular diseases, *Jr Clin Invest*, 1928, v, 343.
- ⁸HURCHINSON, J. On the capacity of the lungs and the respiratory functions, with a view of establishing a precise and easy method of detecting disease by the spirometer, *Med Chir Tr*, 1846, xxix, 137.
- ⁹PEABODY, F. W., and WENTWORTH, J. A. Clinical studies of the respiration, IV. The vital capacity of the lungs and its relation to dyspnea. *Arch Int Med*, 1917, xx, 443.
- ¹⁰BINGER, C. A. L. The lung volume in heart disease, *Jr Exp Med*, 1923, xxxviii, 445.
- ¹¹MEAKINS, J. C., and CHRISTIE, R. V. Lung volume and its variations. *Ann Int Med*, 1930, iii, 423.
- ¹²COHNHEIM, J. and LITTEN, M. Ueber die Folgen der Embolie der Lungenarterien, *Virchow's Arch f path Anat u Physiol*, 1875, lxxv, 99.
- ¹³TOYAMA, K. Experimentelle Forschung ueber die Lungencapillaren, *Ztschr f d ges Exp Med*, 1925, xlv, 168.
- ¹⁴WEARN, J. T., BARR, J. S., and GERMAN, W. J. The behavior of the arterioles and capillaries of the lungs, *Proc Soc Exper Biol and Med*, 1926, xxiv, 114.
- ¹⁵HALL, H. L. A study of the pulmonary circulation by the trans-illumination method, *Am Jr Physiol*, 1925, lxxii, 446.
- ¹⁶WEISS, SOMA, and FRAZIER, W. R. The density of the surface capillary bed of the forearm in health, in arterial hy-

- pertension, and in arteriosclerosis. *Am. Heart Jr.*, 1930, v. 511.
- ¹⁷WEARN, J. T. Personal communications.
- ¹⁸LICHTHEIM, L.: Die Störung des Lungenkreislaufs und ihre Einfluss auf den Blutdruck, 1876, August Hirschwald, Berlin
- ^{19v}BASCH, S. S.. *Allgemeine Physiologie und Pathologie des Kreislaufs*, 1892, Vienne
- ²⁰BLUMGART, H. L., and WEISS, SOMA: Clinical studies on the velocity of blood flow, X The relation between the velocity of blood flow, the venous pressure and the vital capacity of the lungs in fifty patients with cardiovascular disease compared with similar measurements in fifty normal persons, *Jr. Clin. Invest.*, 1928, v. 379
- ²¹ELLIS, L. B., and WEISS, SOMA: The measurement of capillary pressure under natural conditions and after arterial dilatation, in normal subjects and in patients with arterial hypertension and with arteriosclerosis *Jr. Clin. Invest.*, 1929, viii, 47.
- ²²ROBB, G., and WEISS, SOMA: Unpublished observations
- ²³WEISS, SOMA, and BLUMGART, H. L. The effect of the digitalis bodies on the velocity of blood flow through the lungs and on other aspects of the circulation. A study of normal subjects and patients with cardiovascular disease, *Jr. Clin. Invest.*, 1929, vii, 11
- ²⁴HOCHREIN, M., and MEIER, R. Ueber neuere Methoden zur Bestimmung der arteriellen Blutgeschwindigkeit, *Münch. med. Wchnschr.*, 1927, 1995
- ²⁵WEISS, SOMA: Ueber Spontankontraktionen überlebenden Arterien, *Arch. f. d. ges. Physiol.*, 1920, clxxxi, 213.
- ²⁶WEISS, SOMA, and ELLIS, L. B. The circulatory mechanism and unilateral edema in cerebral hemiplegia, *Jr. Clin. Invest.*, 1930, ix, 17.

Dissecting Aneurysms of the Aorta, Including the Traumatic Type: Three Case Reports*

By PAUL C SAMSON, M D,** *Chicago, Ill*

IN DEALING with dissecting aneurysms of the aorta one is confronted with the strange clinical paradox, that a condition which has such marked pathology is so rarely diagnosed during life. Since the lesion was first accurately described by Morgagni¹ in 1761 there have been over four hundred cases, either described or mentioned in the literature. From English and German sources, Gage² has collected only seven cases diagnosed during life. (See Swaine,³ Wyss,⁴ Mager,⁵ Davy and Gates,⁶ Moosberger,⁷ Finny,⁸ and Osler.⁹ Etling¹⁰ refers to five more cases all of the traumatic type, which were diagnosed before death and reports rather fully his own case of traumatic aneurysm of the aorta diagnosed while the patient was still living. (See Grant,^{10a} Bieton,^{10b} Gils,^{10c} Boyer,^{10d} and Marone^{10e}.) To this small group should be added a case diagnosed antemortem by Dr. E. E. Irons, which is being published. The following re-

view contains another case which was diagnosed before death.

Although the term "dissecting" has been popularly ascribed to Laennec, it has been shown by Peacock¹¹ and others that M. Maunoir and Allan Burns both preceded Laennec in their use of the term.

The etiology is varied. 1. Mechanical injury, trauma from without, of special importance in the present review. 2. "Mesarteritis dessicans," first emphasized by Babes and Mionescu¹² as a disease entity and later supported by Whitman and Stein.¹³ This is probably the same condition referred to by Shennan and Pirie¹⁴ in their paper on the subject, although it is not specifically named. There seems to be a number of cases in which such a condition exists. The underlying cause of mesarteritis dessicans is not fully understood. In some cases it seems to be purely a degenerative process and in others an acute streptococcus or staphylococcus infection appears to play a rôle. The most important microscopic changes noted by the above authors are fatty or hyaline degeneration of the interlamellar connective tissue, thinning and rupture of the elastic fibers, atrophy of the smooth muscle. It is believed that where the underly-

*From the Department of Internal Medicine, Rush Medical College, Chicago, Ill.

**James B. Herrick Fellow in Internal Medicine, Rush Medical College, Chicago, Ill. (Fellowship funds come from the endowment established by Dr. Frank Billings, Chicago, Ill.)

ing cause is pure degeneration, increased stress on the medial tissues because of greater distance from the lumen of the vessel, and lessened blood supply, are important factors. 3 A group of factors causing a sudden severe strain on the cardiovascular system, and presumably increased blood pressure excitement, extreme emotional upset, heavy meals, straining and over-exertion in persons not used to great muscular effort. In practically every case of this type a generalized arteriosclerosis forms the common substratum, with such agents acting as precipitating factors. Hypertension, chronic or acute, *per se*, while not a frequent cause of dissecting aneurysm, is implicated at times. Thus Von Schnurben¹⁵ in an analysis of ninety-one cases found that in two, hypertension was the sole causative agent, while it was of primary importance in seventeen more. 4 Congenital. The underlying anomalies include a, thymic-lymphatic constitution with aortic and cardiac hypoplasia, b, aortic stenosis; c, dilatation of the aorta at its origin combined with a thinning of the wall. Microscopically the intima is healthy in these patients. They comprise the youngest group in whom dissecting aneurysms occur.

While it is conceded by most authorities that forces causing a sudden cardiovascular strain and increase in blood pressure do not injure the normal aortic wall of a normal individual, it is believed that such forces may precipitate a dissecting aneurysm in persons having congenital cardiac or aortic anomalies of the type mentioned above.

Most authorities consider syphilis as a rare cause of dissecting aneurysm. Von Schnurben¹⁵ found only one case in which he thought that syphilis was responsible. Further emphasis has been added by Loeschke.¹⁶ He states that syphilis rarely if ever is the direct cause of a dissecting aneurysm, but that it may, if present in conjunction with an aneurysm of this type, aggravate the aneurysm considerably. It is true that there have been several case reports of dissecting aneurysm where syphilis was present, but the number is small enough so that the presence of syphilis might be considered coincidental. It seems probable that a luetic mesaortitis, through an interference with the blood supply leads to a degeneration of the medial fibers, and a somewhat displaced arrangement, saccular aneurysms being the sequel instead of the dissecting type.

The symptomatology has been excellently summarized by Gager.¹⁷ The mode of onset is sudden, following excitement, exertion, or injury. The pain is outstanding, sharp and tearing, generally of higher segmental distribution than in coronary thrombosis. There may or may not be radiation. Because of the progressiveness of the pain and the disturbance of circulation in other organs, a good hint to the diagnosis can be gained. There may be pain in the back, possibly caused by a tearing of the intercostal arteries. Pain in the abdomen suggests a tearing of an intercostal artery with the abdominal vessels torn. The pain may be paroxysmal, occurring in spasms, or it may be continuous, increasing in severity.

feet may follow circulatory disturbance (See Davy and Gates,⁶ Dickinson,¹⁷ Swaine,⁸ Oliver,¹⁸ and Peabody¹⁰) Severe continued pain between the shoulder blades combined with substernal pain is a rather constant finding Findings on examination may include a harsh rumbling bellows' sound over the aorta in the chest or abdomen, a sudden increase in the retro-manubrial dullness, adventitious swellings, and an associated inequality in the blood pressure readings and in the pulses on the two sides of the body X-ray corroboration is important

The diagnosis is based on a study of the symptomatology, and of the past history in an effort to discover an exciting cause When the condition is suspected it may be necessary to make a differential diagnosis from coronary thrombosis because the type of pain is often similar in the two conditions In dissecting aneurysm there is usually a continued cardiac competence and a lack of typical lung findings The blood pressure generally continues at its accustomed level at least for a time, and may be unequal on the two sides of the body With continued dissection the pain has a progressive character not found in coronary thrombosis Electrocardiography may show only various types of irregularities The diagnosis of this condition while the patient is still living is important, because a certain number go on to recovery This can be aided by proper supportive measures if the aneurysm is recognized On the other hand a wrong diagnosis may lead to an exploratory laparotomy, or some other course of treatment equally harmful

The prognosis is grave Crowell²⁰ has estimated that about 65 per cent die almost immediately from complete rupture In another 10 to 15 per cent a sudden death usually occurs in a few days The small number surviving this period have a good chance for recovery In these, the aneurysm may rupture back into the aorta, or more rarely, become a closed sac filled with a clot In both cases the false channel eventually becomes lined with intima and a "healed" aneurysm is the result, usually without sign or symptom Obliteration of the false channel by scar tissue proliferation is extremely rare

The intimal laceration usually occurs in that portion of the aorta which is subjected to the most strain from the constant flow of blood, namely in the origin and ascending portions In Peacock's¹¹ series of eighty cases, over two-thirds showed lacerations in this region From a prognostic point of view these are the gravest Not only are the symptoms severe, but a great majority terminate in a short time with rupture into the pericardial sac In general it may be said that the farther along the aorta the aneurysm occurs, the less alarming are the symptoms and the better is the prognosis for life At the origin of the aorta and in the ascending portion and arch, the initial intimal laceration of spontaneous dissecting aneurysm is usually transverse Elsewhere it is usually longitudinal Practically all of the intimal lacerations of traumatic dissecting aneurysm are transverse or slightly oblique, regardless of where they are found

Traumatic aneurysms of the aorta are practically all dissecting While relatively more rare than the sponta-

neous type, they are being seen somewhat more frequently due to the greater number of industrial and automobile accidents occurring at the present time. About one hundred cases have been reported since 1895. War injuries have been responsible for a number. Although Hubener²¹ has stated that in the case of a traumatic intimal rip which has healed without dissection there can be a saccular aneurysm formed from the stretching of the scar by the constant stress of blood pressure, it is hard to conceive that bodily reparative processes cannot, by connective tissue proliferation, reinforce such an area so that it will not become sacculated. However constantly repeated low grade traumatism may lead to a saccular formation. A case reported by McFadzean²² showed four saccular aneurysms of the abdominal aorta and common iliacs in contrast to a relatively healthy thoracic aorta. This occurred in an old man who had for years been a trapeze and hard bar performer. There was no history of lues and no evidence of it at autopsy. In this case it was considered that the long continued traumatization of the vessels between the bar and the vertebrae or pelvic brim was the sole causative agent.

Traumatic dissecting aneurysm may occur in a healthy aorta, providing the causative force is severe enough. Indeed under certain circumstances a healthy aorta may be torn completely across. Such a case was reported by Copeland,²³ in which there was no external evidence of the cause of death. The reason for the complete rupture was not entirely clear. It might have been due to the tearing action of a

coup. Obviously a force of less intensity is necessary to produce a traumatic dissecting aneurysm in a sclerotic and atheromatous aorta. In these cases the site of laceration seems to be the 'hyaline fibroid' lesion described by Adam,²⁴ which is closely attached to the media in a scar-like formation, and not the sclerotic plaque of the intima which is somewhat loosened from the media.

Traumatic dissecting aneurysm of the aorta is generally formed at the time of the accident or immediately following. It may be produced by several types of injuries. A severe blow on the chest by a large blunt force may be the causative factor. Kuhn²⁵ had under his care a man who was struck in the chest by a block of wood thrown from a buzz saw. A crushing injury of the chest with the fracture of several ribs, such as sustained in an auto accident or in a fall, may be responsible. (See cases below). Sherman has also reported a case in which a fall caused a dissecting aneurysm. The individual struck the pavement, fracturing his clavicle and several ribs.

It has been shown that in traumatic dissecting aneurysm the initial intimal laceration is usually (a) at or near the attachment of the obliterated ductus Botalli, (b) just above the aortic valves. It is often the posterior part of the wall that is injured. It would be remembered that the ligamentum arteriosum joins the aorta very near the root of the left lung, and is closely related to the structure of the root. The whole structure is torn and the blood is forced into the wall of the aorta. The dissection may extend for a distance of several centimeters, and may be fatal.

point The arch as a whole is further fixed by the great arterial trunks In the post-mortem examination of many cases, it has seemed that the hinge-like action of this attachment was responsible for localizing the point of injury This has been emphasized by Jaffe and Sternberg²⁷ and Shennan²⁰ The former authors found that in aviators who had fallen from various heights, there were transverse aortic lacerations at or near this attachment The anterior wall of the aorta is not as fixed as the posterior, and the latter may be crushed against the vertebral column, thus sustaining the brunt of the impact

With regard to the medico-legal aspect, Kauffmann²⁸ maintains that dissecting aneurysms do not form as the immediate effect of an accident, and that the time elapsed is generally great enough to relieve an insurance company of any responsibility He states that a large aneurysm noticed after an accident generally speaks against any relationship between the aneurysm and the accident On the other hand, Etling¹⁰ has collected evidence to support the opposite view The judgments rendered in his cases show that 1 Traumatism is admitted to be a cause of dissecting aortic aneurysm, 2 The lesion is very serious, 3 When it occurs while at work and is so diagnosed, it may constitute the basis for damage-suits and claims for compensation, 4 Treatment should be continued over several months before an amelioration of symptoms is hoped for, 5 When symptoms persist the lesion may be classified under the law allowing for accidents from work, 6 In point of gravity traumatic aneurysms

should be placed among the causes for permanent incapacity from work

In at least one instance²⁹ in this country, a Supreme Court (here of Idaho) has ruled that when a sudden strain or injury on the part of an individual during the course of employment either causes a fatal dissecting aneurysm or aggravates one already present to such an extent that the patient dies, such a fatality constitutes a death from an accidental injury and is compensable

CASE REPORTS

The first case is rather unusual While not absolutely proven, it is believed that the dissecting aneurysm found at autopsy was of traumatic origin It was undiagnosed during life, was symptomless, and played no rôle in the death of the patient The aneurysm had occurred sometime previously, probably dating back five years to the time of the patient's rather severe injury While it ended in a blind pocket and had not ruptured back into the aorta, the aneurysm was "healed" in the sense that it was entirely lined by endothelium and had a small blood stream functioning through a canalized thrombus which supplied the superior mesenteric and left renal arteries

CASE 1 C W, a white man, age 73, until five years before his death had enjoyed excellent health At that time, in the fall of 1925, he was in an automobile accident The hospital report, furnished by Mercy Hospital, Oshkosh, Wisconsin, showed that he was admitted in an unconscious condition General examination and x-ray, revealed an oblique fracture of the right clavicle with displacement, three transverse fractures of the sternum in fair position, and fractures of the mid-portions of the 3rd and 4th ribs on the right

While in the hospital the patient had some blood stained sputum, but no frank hemoptysis. The first urine specimen was smoky and full of microscopic blood. Albumin and many casts were present. The blood Wassermann was negative. There was a temperature rise to at least 100° F, nearly every day. The patient was in the hospital three weeks. He was not well following discharge, but suffered considerable pain in his hips and lower spine. In Dec., 1926, he went to the Mayo Clinic. The abstracted record shows that he was suffering from a hypertrophic arthritis of the hip joints. His fractures had healed. There was some hypertension and a moderate secondary anemia. Urinalysis and blood Wassermann were negative. There was a generalized sclerosis of the pelvic vessels. No heart disease was reported. According to his daughter he had not suffered any shortness of breath or pain up to this time. Several months later he became weak and short of breath after walking against a wind. This passed off with rest. In January, 1930, his ankles began to swell and his liver became enlarged. A week of low grade abdominal pain and slight shortness of breath was followed by an attack of extreme dyspnea, and a sudden excruciating epigastric pain. This lasted some time. After a month's sickness he recovered temporarily and started to do a little work again. He did not limit himself sufficiently, and in May, 1930, he had a similar attack. He never completely recovered, and for the next five months before his admission to Presbyterian Hospital, he suffered considerably from dyspnea and dull epigastric pain. Latterly he took morphine nightly for rest and was not able to leave the house. He could lie down but rested more easily on pillows.

He was admitted in August, 1930, on the service of Dr R C Brown. There was grave cardiac decompensation. The heart was enlarged, rate 60, with marked irregularity and a moderate pulse deficit. His respirations were labored and of Cheyne-Stokes' type. There were a few moist râles at the bases, the liver was enlarged and the lower extremity edema reached to the knees. There was a moderate secondary anemia. His blood chemistry was normal. The blood

pressure was 168 over 102. The urine admission showed albumin and casts, which however, cleared up before discharge. A phenolsulphonphthalein test showed a 60 per cent excretion in three hours. The electrocardiogram showed myocardial damage: ventricular extra-systoles. He was in hospital for two and one half weeks on usual supportive régime and showed marked clinical improvement. He remained at home for five weeks. On re-admission all previous symptoms were aggravated and grew gradually worse until his death days after admission. His rather sudden death was typically cardiac. The clinical diagnosis was arteriosclerosis with moderate hypertension, chronic fibrous myocardium and cardiac decompensation, and general anasarca.

Post-mortem Examination (Dr C H felbach) "Anatomical Diagnosis: Marked generalized arteriosclerosis, multiple infarcts of the myocardium, marked hypertrophy of the wall of the left ventricle, chronic passive hyperemia, marked anasarca of the lower extremities, ascites and bilateral hydrothorax, arteriosclerotic atrophy of the kidneys, old dissecting aneurysm (traumatic) of the thoracic portion of the aorta.

"The aorta was opened along the dorsal wall. The scissors, cutting from the top downward, entered a sac. The beginning of the sac was 14 cm above the mouth of the celiac axis. At its upper end there was a transverse groove in the lining of the sac about 1 mm wide. The main channel of the aorta consisted of a narrow curved passage that admitted a thin metal ruler 1 cm wide, the upper opening of the sac being at least four-fifths of a cross-section of the aorta. The narrow true posterior channel of the aorta was on the right side of the sac (Figure 1*). The lower end of the posterior channel was at the mouth of the posterior arteries, and into it also opened the posterior arteries and the celiac axis. The sac was about 16 cm long, the proximal part being filled with fluid blood, and the distal 10 cm was occupied by the

*The photographs are by Mr F H felbach, photographer at Rush Medical College, under the supervision of Dr C H felbach.



FIG 1 The true channel of the aorta is at the right side and the opening is held together artificially. The proximal portion of the aneurysmal sac contained only fluid blood, whereas the distal portion, where it bulged slightly, is filled by a canalized thrombus. In the true channel of the aorta the mouth of the right renal artery is visible immediately adjoining the wall of the aneurysm near the distal end of the sac.

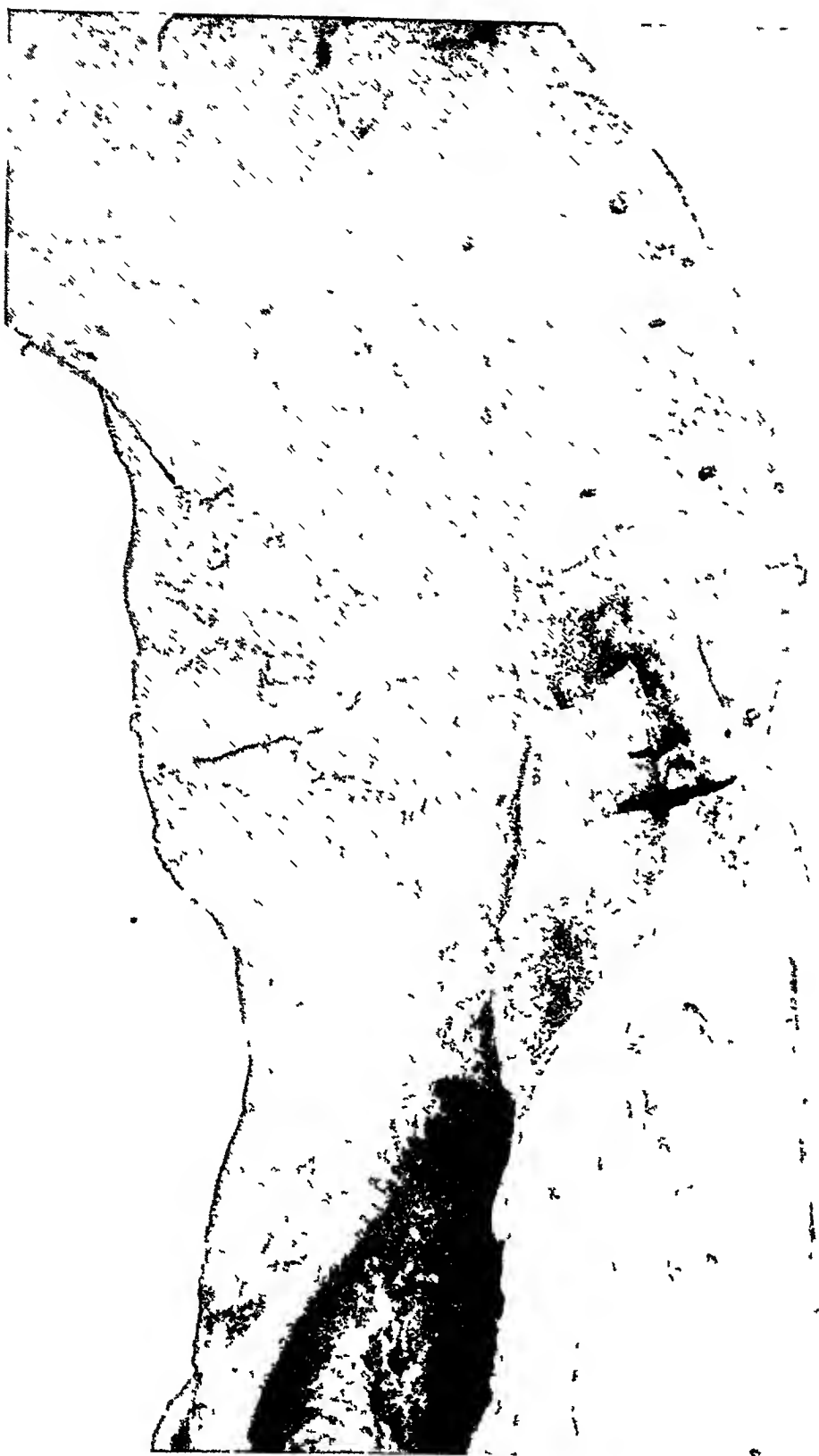


FIG 2 Illustration of the transverse scar and the ridge of tissue stretching across part of the opening of the aneurysm. The lining of the first part of the aneurysm is irregular, but there are no fatty changes like those in the wall of the upper portion of the aorta or of the true passage.

tion with the daughter, did he have any symptoms indicative of a spontaneous dissecting aneurysm of the size found, in which there must have been a temporary but serious interference with the blood supply to the left kidney and small loops of bowel. Immediately following the accident the patient had a smoky hematuria, probably from the kidney. Hanser³⁰ has emphasized dissecting aneurysm as a cause of blood in the urine, of renal origin. The train of symptoms and the cardiac failure responsible for his death are explainable on the basis of the coronary thrombosis found at autopsy. The original intimal laceration was in the upper part of the descending thoracic aorta and was transverse. If the aneurysm had been present previously, it would have in all probability ruptured through at the time of the accident. There was no blood staining of the tissues in the neighborhood of the scar either microscopically or macroscopically. Under similar circumstances, if the indi-

vidual in question had been younger and without atherosclerosis, the diagnosis of *traumatic* dissecting aneurysm would have been unquestioned.

CASE 2 This case was also believed, from rather positive clinical and x-ray evidence, to have been one of traumatic dissecting aortic aneurysm, and was so diagnosed during life. There was no post-mortem proof, however. *History* Dr R. A. W., age 62, was admitted to the Presbyterian Hospital on the service of Dr. James B. Herrick in July, 1922. He complained of tachycardia, dyspnea on exertion, orthopnea, and swelling of the ankles.

Eleven years before at the age of 51, when previously perfectly well, he had fallen on his back from a height of ten feet. He was severely shaken up and following the fall he had hemoptysis for three weeks. During this time he suffered from a severe substernal pain and sense of oppression. The pain went through to his back. Later it became constant and aching.

A year after the accident he had his first attack of tachycardia, weakness and dyspnea, coming on suddenly while operating. Fluoroscopy showed a slightly dilated pulsating aorta. Two years after the accident x-ray showed a definite fusiform aneurysm.

of the descending thoracic aorta. There was no history of lues and repeated Wassermann examinations were negative. Three years after the accident the patient had a similar attack, again while operating. Between attacks he was symptom free. During the seven years previous to his admission to Presbyterian Hospital, he had attacks of tachycardia, coming on about once a month, generally without exertion. His blood pressure averaged about 160 over 100. There was a slight albuminuria discovered nine years before.

The patient had been able to work until May, 1922, in spite of his attacks, but at that time he had a particularly bad spell, associated with a dilated heart. He rested during the four months previous to his ad-

mission, but in spite of this there was a progressive increase in the severity of his symptoms.

On admission, general examination showed a somewhat enlarged heart, and an increase in the retromanubrial dullness. No murmurs were heard. There was a systolic retraction of the precordial interspaces. The liver was enlarged but there was no ascites. Some edema of the legs was present. Urinalysis showed albumin and casts. X-ray showed a fusiform dilatation of the descending thoracic aorta.

While in the hospital there was a progressive improvement, and the patient was discharged with a diagnosis of "healed" traumatic dissecting aneurysm of the descending thoracic aorta, adhesive pericarditis.



FIG 4 This is a transverse section through the distal third of the aneurysm illustrating the canalization of the large thrombus which occupies the false channel, and the splitting of the media to form the wall of the aneurysm. The aortic channel is on the left.

and pleuritis, chronic myocarditis with broken compensation, and chronic nephritis. The patient lived some time after discharge from the hospital

CASE 3 Through Dr E. R. LeCount it was learned that Dr. Roger T. Vaughan, Night Warden at Cook County Hospital, had diagnosed a case of spontaneous dissecting aneurysm of the aorta during life. Aside from the obvious interest attached to a rare diagnosis, this case is important because it illustrates, also, the all too frequent tendency to diagnose a perforated ulcer because of acute upper abdominal pain.

Case Summary J. H., a white male, age 49, was admitted to Cook County Hospital in December, 1921, at 6 P. M., after having been seen at home and sent in as a suspected case of perforated gastric ulcer. Previous to this time there had been trouble referable to the gastro-intestinal tract. However he had complained of palpitation on climbing stairs for about two months. Six weeks before the onset he had been treated at the Rush Dispensary for "heart trouble."

About five hours before admission and shortly after eating, he was suddenly seized with an agonizing knife-like pain, located principally in the epigastrium. It was constant, but waxed and waned in intensity. It doubled him up and he was very restless, rolling from side to side. The pain was something entirely new to him. He vomited several times during the afternoon, but had seen no blood. He was dizzy and covered with perspiration. Earlier, his distress had been aggravated by drinking hot water. On admission there was slight upper abdominal rigidity and moderate tenderness localized chiefly in the epigastrium. The pain was entirely out of proportion to these

rough to and fro pericardial friction rub was audible over the entire precordium. There was a retraction of the apical interspaces in systole. The lung examination was negative. On careful questioning it was elicited that the patient also had pain over the lower two or three ribs on both sides, radiating from back to front.

The conclusion drawn was that this was not a surgical abdominal condition. The absence of marked rigidity, tenderness, distension, and mass and the presence of practically normal peristaltic sounds failed to form the basis of any evidence of an intra-abdominal lesion.

The primary findings were severe pain in the epigastrium and lower chest, neuralgiform in character, sudden in onset, and lasting more or less constantly over a period of five hours, unequal pulses and unequal blood pressures. Along with the slight anemia this suggested a sudden accident in the chest. At his age the rupture of an aneurysm was the most likely possibility, and the relative slowness of a fatal termination suggested an aneurysm of the dissecting variety. There was no evidence of perforation into the peritoneal or pleural cavities. No aneurysmal findings such as bruit or pulsation were present. It was suspected then that the lesion was an aneurysm of the arteriosclerotic type affecting

mission prohibited such a procedure. In addition it was felt that the diagnosis was sufficiently secure on clinical grounds alone. Post-mortem examination was confirmatory.

Anatomic Diagnosis (Dr E R LeCount)

"Fresh dissecting aneurysm of the aorta, innominate and right common carotid arteries perforation into the pericardial sac, marked hemopericardium, slight left hemothorax, slight hemoperitoneum, slight hemorrhage into the tissues back of the aorta and around the innominate artery and vein, compressed right auricle and ventricle, edema and anemia of the lungs, edema and marked hyperemia of the liver, passive hyperemia of the kidneys and spleen."

Other items in the diagnosis have no bearing on the disease under discussion.

"The pericardial sac is completely filled with blood, most of which is clotted. The pulmonary artery is deeply furrowed by the pressure in front, and the right auricle and ventricle are partially collapsed. The hemorrhage has occurred from a rupture of the adventitia on the right side of the aorta. In addition to the pericardial hemorrhage, blood has seeped into the tissues just below the innominate vein and to the left of the innominate artery. There is a slightly turbid pale brown fluid in the left pleural cavity."

The wall of the aorta is split all the way down to 4 cm caudad to the renal arteries and the split extends in the other direction to the heart and is in the dorsal part of the wall. The wall of the abdominal aorta is thin, and occupying nearly all of the lining of this part, as well as of the common iliacs, are yellowish thickenings without lime. The dissection is continued into the innominate and right common carotid arteries, but these are the only branches so involved. The split in the innominate artery extends into the right common carotid artery for about 2 cm distal to the mouth, and here there is a transverse slit in the wall about 7 mm long, through which the lumen of the artery communicates with the aneurysm."

SUMMARY

1 In the foregoing review we have summarized what appear to be the most important features of dissecting aneurysm of the aorta, from a clinical and pathological standpoint.

2 The etiology, symptomatology, diagnosis, prognosis and pathology of dissecting aneurysm of the aorta are given.

3 Particular stress is laid upon traumatism as an etiologic agent, with a discussion of the probable relationships of the different mechanical and anatomic factors concerned.

4 Various medicolegal aspects of traumatic dissecting aneurysm of the aorta are presented.

5 Three new cases are reported, two of which were confirmed at autopsy.

Case 1, illustrated, was probably of traumatic origin. Case 2, probably also of traumatic origin, was diagnosed before death. There was no post-mortem examination. Case 3 was a proven case of spontaneous dissecting aneurysm of the aorta, diagnosed before death.

I am indebted to the following men for timely suggestions, and for permission to use material: Dr James B Herrick, Dr E R LeCount, Dr C W Apfelbach, Dr R C Brown, Dr Roger T Vaughan. Case records and abstracts were kindly furnished by Presbyterian Hospital, Chicago, Cook County Hospital, Chicago, Mercy Hospital, Oshkosh, Wisc., The Mayo Clinic, Rochester, Minn.

REFERENCES

- ¹MORGAGNI De Sedibus, 1761 (Quoted by Gager)
- ²GAGER, L. T. Ann Int Med, 1928-29, 11, 658
- ³SWAINE Trans Path Soc London, 1856, vii, 106
- ⁴WYSS, O. Arch der Heilk, 1869, x, 490
- ⁵MAGYR Ztschr f Heilk, 1903, xxiv, 323
- ⁶DAVY and GATES Brit Med Jour, 1922, 1, 471
- ⁷MOOSBERGER Schweiz Med Wchnschr 1924, liv, 325
- ⁸FINNY Lancet, 1885, 11, 69
- ⁹OSLER Mod Med, Phila, 1908, iv, 468
- ¹⁰ETLING, R. Thèse pour Doctorat en Médecine, Paris Thèses, 1904-05, No 98
- ^{10a}GRANT Austral Med Jr, 1888, x, 393
- ^{10b}BRETON Arch de Med et Pharm Mil, 1891, xviii, 58
- ^{10c}GILS Loc cit, 1893, xxii, 122
- ^{10d}BOYER Lyon Med, July 10, 1904
- ^{10e}MARONE Riforma Med, 1897, 1, 386
- ¹¹PLACOCK, Trans Path Soc London, 1862-63, xiv, 87.
- ¹²BABIS, V. and MIROVLSCU, Th Beitr z path Anat, 1910, xlvii, 221
- ¹³WHITMAN and STLIN, J. Jr Med Research, 1923-24, xlv, 579
- ¹⁴SHENNAN, T., and PIRRI, J. H. Brit Med Jr, 1912, 1, 1287
- ¹⁵VON SCHNURBLIN Frankf Ztschr f Path, 1926, xxxiv, 532
- ¹⁶LOESCHKE, A. Frank Ztschr f Path 1928, xxxvi, 56
- ¹⁷DICKINSON Trans Path Soc London 1862, xiii, 48
- ¹⁸OLIVER Lancet, 1892, 1, 1068
- ¹⁹PEABODY Med Record, N Y, 1889, xviii, 326
- ²⁰CROWELL, P. D. Jr Am Med Assoc 1921, lxxvii, 2114
- ²¹HUBENER Monatsschr f Unfallh 1928, xxxv, 342
- ²²McFADZEAN, J. Brit Med Jr, 1928, 11, 154
- ²³COPELAND, G. G. Jr. Am Med Assoc, 1914, lxiii, 1950
- ²⁴ADAMI, J. G. Mont Med Jr 1895, xxiv, 945, 1896, xxv, 23
- ²⁵KUHN, L. P. Ill Med Jr, 1925, xlvii, 420
- ²⁶SHENNAN, T. Jr Path. and Bact, 1920, xxxii, 795
- ²⁷JARRI, R. II, and STERNBERG. Verhshch f gerichtl Med, 1919, lviii, 71
- ²⁸KAUFMANN Monatsschr f Unfallh. 1929, xxxvi, 182
- ²⁹LARSON v BLACKWELL LUMBER Co (Idaho 279, 1987), from Jr Am Med Assoc, 1930, xciv, 1520
- ³⁰HANSIR, A., Deutsch Arch f klin Med 1926, cli, 61

Clinical and Experimental Observations on the Treatment of Pernicious Anemia with Desiccated Stomach and with Liver Extract*†

By CYRUS C. STURGIS, M.D., F.A.C.P., and RAPHAEL ISAACS, M.D.,
F.A.C.P., *Ann Arbor, Michigan*

INTRODUCTION

THE possibility that a defect in the stomach may be related to the etiology of pernicious anemia has been recognized for many years. This belief has been based upon a number of clinical facts, some of which have been established and confirmed by numerous observers. The most significant evidence suggesting this etiological relationship is that every patient, probably without exception, has at least a functional impairment of the stomach mucosa as indicated by the inability to secrete hydrochloric acid. This fact becomes even more significant now that it is known that hydrochloric acid is not secreted under the powerful stimulus of histamin injections, that the achlorhydria precedes all other known evidence of the disease, and that the acid does not appear in the gastric contents during a spontaneous or therapeutically induced remission. Evidence of an impaired function of the stomach mucosa, therefore, is the

earliest, the most constant, and the most persistent abnormality known to exist in a patient with the disease.

Additional suggestive data pointing to the rôle of the stomach in the causation of the disease, are to be found in the reported cases of patients who have had a total gastrectomy and who later developed the blood picture of pernicious anemia. This important evidence is based upon only rare observations, as the operation usually is performed for extensive carcinoma of the stomach, recurrences of the growth may confuse definite conclusions, and many patients do not survive a sufficient period of time to permit the development of the anemia.

Opinions concerning the importance of the stomach in the etiology of pernicious anemia have been based solely upon clinical observations until recently when Castle¹ reported his classical experiments, which appear to demonstrate conclusively that there is fundamental relationship between the anemia and a defect in the gastric secretion. This observer fed proteins in the form of 300 grams of slightly cooked Hamburg steak to normal persons and recovered it after it had been

*From the Thomas Henry Simpson Memorial Institute for Medical Research, University of Michigan, Ann Arbor, Michigan.

†Read at the Baltimore Meeting of the American College of Physicians, March 27, 1931.

the sex, age, duration of present illness, red blood cell count prior to treatment and the dosage employed in treatment in the two groups is given in Table I

Preparations Used and Method of Administration—The desiccated stomach* was prepared by removing the fat and surrounding mesentery, and chopping the material very fine. This was then dried at a low temperature and the fat removed by repeatedly washing with petroleum benzine. One hundred grams of fresh stomach yielded an average of 13.3 grams (11.7 to 15.0 grams) of the dried, defatted, material. With the fat removed the material has very little odor and only

*Ventriculin (N.N.R.) prepared through cooperation with Parke, Davis and Company of Detroit

a slight taste. It is not soluble in water, but may be eaten, preferably in tomato juice, as one would a thick cereal. Lilly's Liver Extract was used throughout in the second group and in most instances was given in tomato juice, but also in water or orange juice. Usually both therapeutic agents were given to the patient midway between breakfast and lunch, but occasionally the dose was divided into two equal parts by giving a mid-morning and mid-afternoon portion.

The blood studies were made at the same time each day so that comparative observations could be recorded. For the reticulocyte counts, brilliant cresyl blue-Wright's stain preparations were made, 1000 cells being counted, except when there was any doubt, in which case 2,000 or more were enumer-

TABLE I

	Fifty patients treated with desiccated stomach—(Ventriculin)		Fifty patients treated with Lilly's Liver Extract	
Sex	Males 31	Females 19	Males 34	Females 16
Age	40 to 70 years (92%) 40 to 60 years (68%) 3 under 40 years (24, 26, 27 years) 3 over 70 years (72, 74, 74 years)		40 to 60 years (56%) 40 to 70 years (80%) 3 under 40 years (34, 35, 39 years) 5 over 70 years (72, 73, 74, 74, 75 years)	
Duration of illness	1 year or less	50%	1 year or less	46%
	2 years or less	62%	2 years or less	62%
	3 years or less	96%	3 years or less	80%
	Over 3 years	4%	Over 3 years	20%
Red blood cell count before treatment	1 million or less	12%	1 million or less	28%
	1.1 to 2 million	58%	1.1 to 2 million	50%
	2.1 to 2.8 million	30%	2.1 to 2.8 million	22%
Dosage	80% of patients received 30 to 40 grams daily 10% of patients received 15 to 20 grams daily		68% of patients received from 5 to 12 vials* daily 18% of patients received from 3 to 4 vials daily	

*1 vial is made from 100 grams of liver

however, may persist in those patients who have advanced spinal cord changes, even though the red blood cell count becomes normal. It is possible that this may be explained by an impairment of the nervous control of the intestines. The characteristic glossitis which was present in over fifty per cent of this group of patients is usually readily controlled by the treatment. In a few patients, it has persisted in a mild degree, and occasionally there has been recurrence of the complaint after the blood has become normal.

Fever, Pulse Rate, Gain in Strength
Other striking manifestations of improvement are the disappearance of the

fever and tachycardia which are so commonly present when the anemia is severe, and a rapid gain in strength and sense of well being. Even when the anemia has been severe before treatment, the patient is usually able to become ambulatory within a week or two, and in an additional six to eight weeks may resume a normal life. Some patients have returned to their former laborious occupations, which have required more than an ordinary amount of physical strength and endurance.

Skin Changes Additional and constant evidence of improvement is a disappearance of the yellowish pallor which is present in all patients when

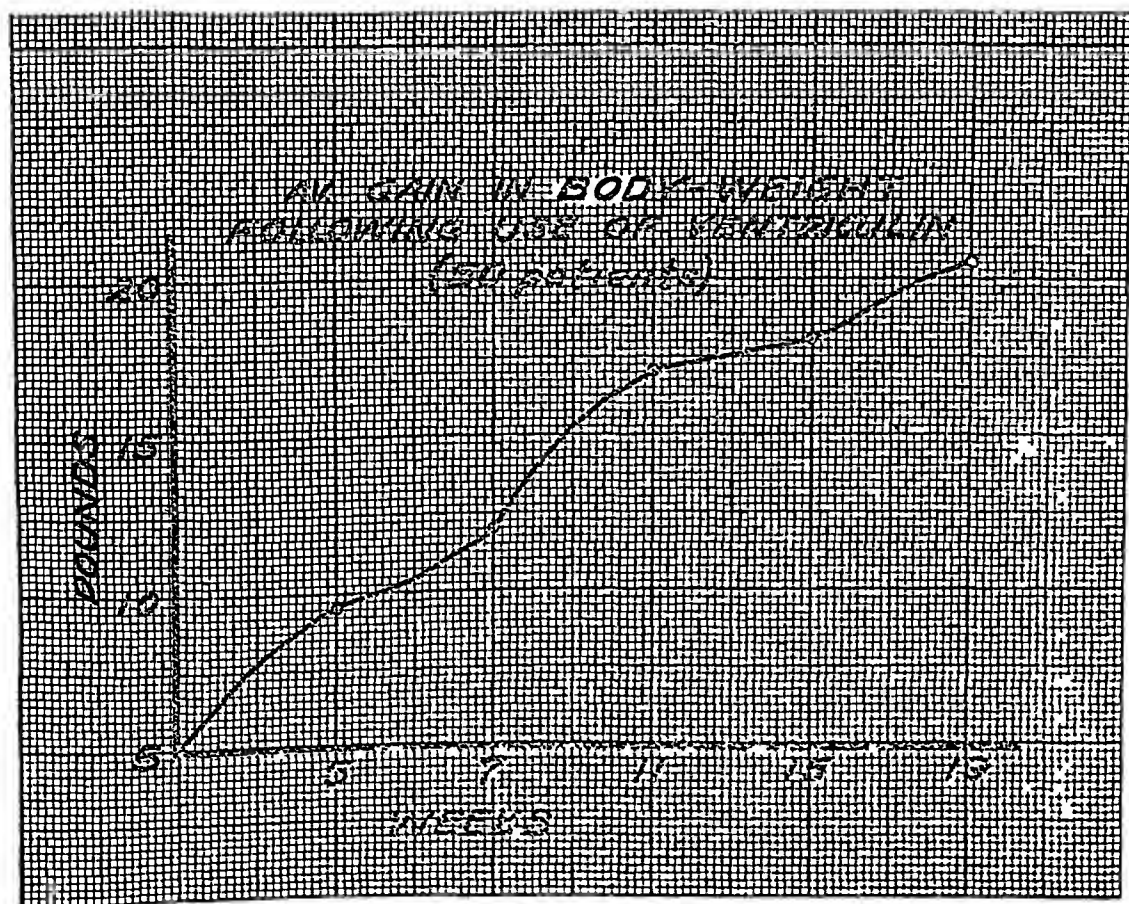


FIG 1 Shows average gain in body weight of 50 patients treated with Ventriculin, in weeks

the anemia is severe. This disappears as the blood bilirubin approaches normal, which is in about two or three weeks. It is interesting to note that within a few days after the treatment is begun, the pads of the fingers and palms, the chin, the cheeks and the tip of the nose become flushed. This reaction must be a vasomotor phenomenon as the flushing occurs before there is a demonstrable increase in the red blood cell count. The creases in the palm of the hands remain pale, however, and do not become red until the blood count is between $2\frac{1}{2}$ and 3 million red blood cells per cubic millimeter.

tract to keep their blood at a normal level. From our present experience, however, it is not possible to say that desiccated stomach is superior to liver in treating the neurological complications. In general it may be concluded that improvement in the minor neurological symptoms frequently occurs, but in patients with more extensive involvement, the outlook is far less promising.

CHANGES IN THE PERIPHERAL BLOOD

When desiccated defatted whole stomach or liver or liver extract is fed to patients with uncomplicated pernicious anemia, a characteristic "reticulocyte response" follows. This consists of (1) a latent period, (2) a rapid increase in the absolute number and percentage of reticulocytes, reaching a maximum, followed by (3) a decrease in the percentage until the pretreatment level or slightly above (1 to 3 per cent) is reached.

Maximum reticulocyte

$$\text{per cent} = \frac{0.73 - 0.2 E^{\circ}}{0.73 + 0.8 E^{\circ}}$$

(E° = Initial red blood cell count in millions
per cu mm)

The following table shows the calculated maximum reticulocyte percentage with relation to the initial red blood cell count.

TABLE II

Initial Red Blood Cell Count*	Range of Maximum Reticulocyte Percentage	Average Maximum Reticulocyte Percentage
04	55.7 - 69.1	61.9
05	50.4 - 61.9	55.7
06	45.7 - 55.7	50.4
07	41.6 - 50.4	45.7
08	38.0 - 45.7	41.6
09	34.6 - 41.6	38.0
10	31.7 - 38.0	34.6
11	29.0 - 34.6	31.7
12	26.5 - 31.7	29.0
13	24.3 - 29.0	26.5
14	22.3 - 26.5	24.3
15	20.4 - 24.3	22.3
16	18.7 - 22.3	20.4
17	17.1 - 20.4	18.7
18	15.6 - 18.7	17.1
19	14.1 - 17.1	15.6
20	12.9 - 15.6	14.1
21	11.6 - 14.1	12.9
22	10.5 - 12.9	11.6
23	9.4 - 11.6	10.5
24	8.4 - 10.5	9.4
25	7.5 - 9.4	8.4
26	6.6 - 8.4	7.5
27	5.7 - 7.5	6.6
28	4.9 - 6.6	5.7
29	4.1 - 5.7	4.9
30	3.4 - 4.9	4.1
31	2.7 - 4.1	3.4
32	2.1 - 3.4	2.7
33	1.5 - 2.7	2.1
34	0.9 - 2.1	1.5
35	0.3 - 1.5	0.9

*Millions per cubic millimeter

The average actual maximum reticulocyte per cent for the hundred patients treated by liver or stomach was 23.7. The calculated maximum for this group was 21.52 per cent. For the 50 patients treated with liver extract the actual maximum was 22.36 per cent, while the calculated maximum was 23.43 per cent. For the 50 patients treated with desiccated stomach, the observed maximum was 24.19 per cent, while the calculated maximum was 19.61 per cent.

Figure 2 shows the relationship between the observed maximum reticulocyte percentage and the initial red blood cell count compared to the calculated maximum percentage for the liver extract cases and for those treated with stomach. It is evident that the patients receiving Ventriculin made from an average of 225 grams of fresh stomach daily responded as well as, if not better than, those receiving the extract made from an average of 536 grams of fresh liver daily. If whole liver and whole stomach have the same degree of hemogenic activity, one-half of it must be lost in making the liver extract.

Of the 50 patients treated with liver extract, the average length of time required to reach the maximum reticulocyte percentage was 6.9 days, while the average for the stomach treated patients was 7.52 days, a difference of a little more than one-half day. This was exclusive of patients receiving massive doses. In view of the fact that the stomach treated patients reached, and in many cases exceeded, the calculated maximum reticulocyte percentage, the 0.62 day increase in

the anemia is severe. This disappears as the blood bilirubin approaches normal, which is in about two or three weeks. It is interesting to note that within a few days after the treatment is begun, the pads of the fingers and palms, the chin, the cheeks and the tip of the nose become flushed. This reaction must be a vasomotor phenomenon as the flushing occurs before there is a demonstrable increase in the red blood cell count. The creases in the palms of the hands remain pale, however, and do not become red until the blood count is between $2\frac{1}{2}$ and 3 million red blood cells per cubic millimeter.

CHANGES IN THE NERVOUS SYSTEM

A very large majority of patients with pernicious anemia have symptoms referable to the nervous system of which the most common is paresthesia of the hands and feet. This symptom may entirely disappear with stomach therapy, although it is not entirely controlled in all patients. There is a less favorable effect on the more serious neurological complications, such as loss of the sense of position of the limbs, impaired control of the sphincters of the bladder and rectum, and spastic paraplegia, although occasionally the improvement may be remarkable. In some instances, the neurological manifestations are held in abeyance, or, less commonly, there may be a distinct advance in the symptoms despite the fact that the anemia has been controlled. The latter situation has not been observed so far in patients who have been treated with desiccated stomach, but has been known to occur in those who have received sufficient liver ex-

tract to keep their blood at a normal level. From our present experience, however, it is not possible to say that desiccated stomach is superior to liver in treating the neurological complications. In general it may be concluded that improvement in the minor neurological symptoms frequently occurs, but in patients with more extensive involvement, the outlook is far less promising.

CHANGES IN THE PERIPHERAL BLOOD

When desiccated defatted whole stomach or liver or liver extract is fed to patients with uncomplicated pernicious anemia, a characteristic "reticulocyte response" follows. This consists of (1) a latent period, (2) a rapid increase in the absolute number and percentage of reticulocytes, reaching a maximum, followed by (3) a decrease in the percentage until the pretreatment level or slightly above (1 to 3 per cent) is reached.

CALCULATED MAXIMUM RETICULOCYTE PER CENT

A valuable feature in studying the potency of a preparation is the height to which the reticulocyte percentage increases after the therapy has been started. Based on the study of the average maximum rise reached in many patients, Minot, Cohn and their co-workers⁴ noted that there was a relationship between the maximum height of the reticulocyte count and the initial red blood cell count. The lower the red blood cell count on the day that the first dose of the medicine was given, the higher was the rise in the number of reticulocytes. Riddle's formula⁵ is as follows:

Maximum reticulocyte

$$\text{per cent} = \frac{0.73 - 0.2 E^{\circ}}{0.73 + 0.8 E^{\circ}}$$

(E° = Initial red blood cell count in millions per cu mm)

The following table shows the calculated maximum reticulocyte percentage with relation to the initial red blood cell count

TABLE II

Initial Red Blood Cell Count*	Range of Maximum Reticulocyte Percentage	Average Maximum Reticulocyte Percentage
0.4	55.7 - 69.1	61.9
0.5	50.4 - 61.9	55.7
0.6	45.7 - 55.7	50.4
0.7	41.6 - 50.4	45.7
0.8	38.0 - 45.7	41.6
0.9	34.6 - 41.6	38.0
1.0	31.7 - 38.0	34.6
1.1	29.0 - 34.6	31.7
1.2	26.5 - 31.7	29.0
1.3	24.3 - 29.0	26.5
1.4	22.3 - 26.5	24.3
1.5	20.4 - 24.3	22.3
1.6	18.7 - 22.3	20.4
1.7	17.1 - 20.4	18.7
1.8	15.6 - 18.7	17.1
1.9	14.1 - 17.1	15.6
2.0	12.9 - 15.6	14.1
2.1	11.6 - 14.1	12.9
2.2	10.5 - 12.9	11.6
2.3	9.4 - 11.6	10.5
2.4	8.4 - 10.5	9.4
2.5	7.5 - 9.4	8.4
2.6	6.6 - 8.4	7.5
2.7	5.7 - 7.5	6.6
2.8	4.9 - 6.6	5.7
2.9	4.1 - 5.7	4.9
3.0	3.4 - 4.9	4.1
3.1	2.7 - 4.1	3.4
3.2	2.1 - 3.4	2.7
3.3	1.5 - 2.7	2.1
3.4	0.9 - 2.1	1.5
3.5	0.3 - 1.5	0.9

*Millions per cubic millimeter

The average actual maximum reticulocyte per cent for the hundred patients treated by liver or stomach was 23.7. The calculated maximum for this group was 21.52 per cent. For the 50 patients treated with liver extract the actual maximum was 22.36 per cent, while the calculated maximum was 23.43 per cent. For the 50 patients treated with desiccated stomach, the observed maximum was 24.19 per cent, while the calculated maximum was 19.61 per cent.

Figure 2 shows the relationship between the observed maximum reticulocyte percentage and the initial red blood cell count compared to the calculated maximum percentage for the liver extract cases and for those treated with stomach. It is evident that the patients receiving Ventriculin made from an average of 225 grams of fresh stomach daily responded as well as, if not better than, those receiving the extract made from an average of 536 grams of fresh liver daily. If whole liver and whole stomach have the same degree of hemogenic activity, one-half of it must be lost in making the liver extract.

Of the 50 patients treated with liver extract, the average length of time required to reach the maximum reticulocyte percentage was 6.9 days, while the average for the stomach treated patients was 7.52 days, a difference of a little more than one-half day. This was exclusive of patients receiving massive doses. In view of the fact that the stomach treated patients reached, and in many cases exceeded, the calculated maximum reticulocyte percentage, the 0.62 day increase in

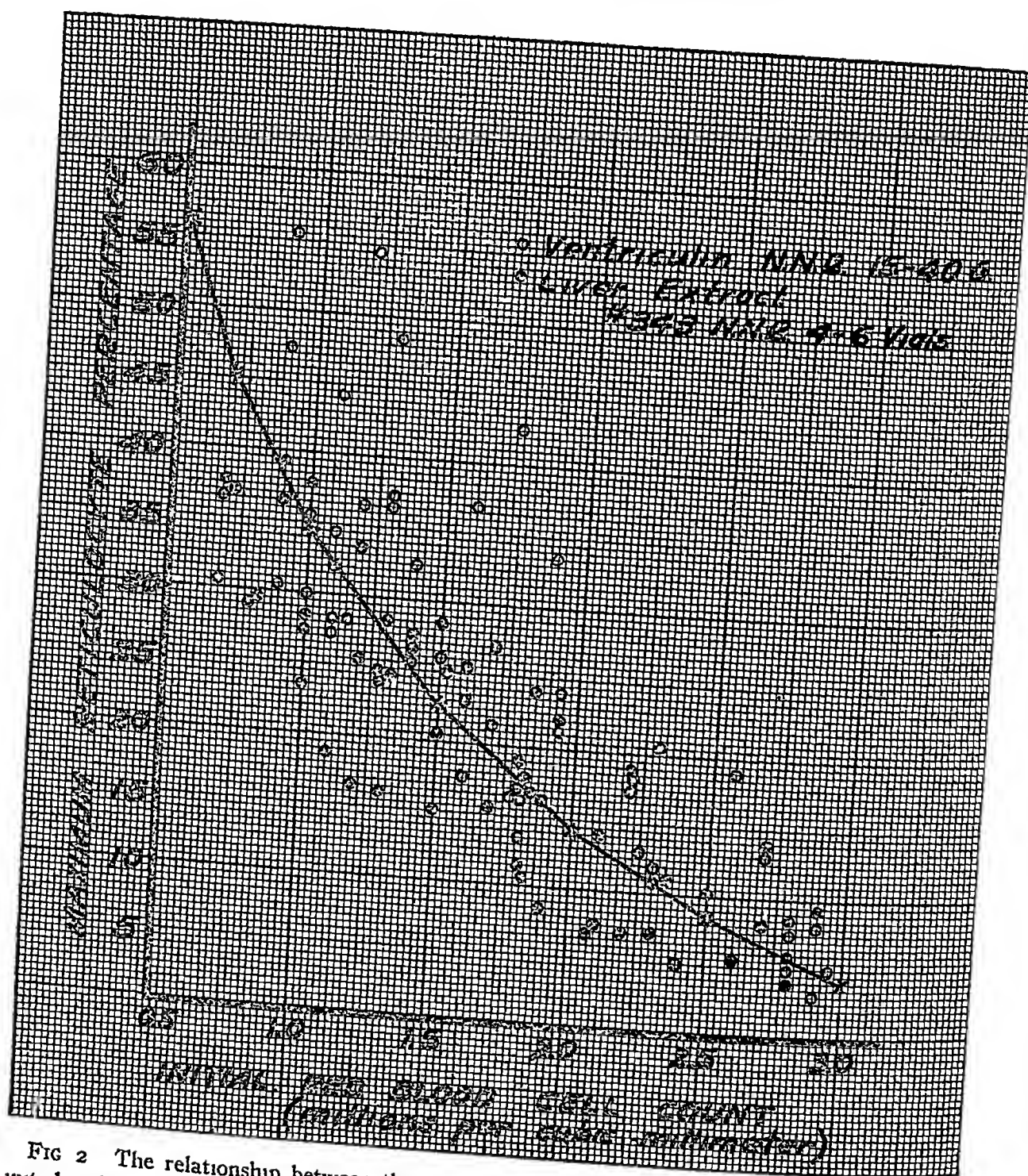


FIG 2 The relationship between the observed maximum reticulocyte percentage and the initial red blood cell count compared to the calculated maximum percentage for the liver extract cases and for those treated with stomach

length of time to reach the maximum must be interpreted not as deficient potency, but as evidence of a longer period required to utilize and absorb the stomach tissue. The liver extract is soluble in water, whereas the stomach tissue is not. Some of the active

substance produced by the stomach tissue may be generated after the dried material has been ingested. Two lines of evidence suggest that this may be a factor, although not the only one. First, in patients in whom there is retention of gastric contents, with slow absorp-

tion, the reticulocyte response is delayed or submaximal

1 Man (No 233076), age 67 years There was considerable retention of food in the stomach 15 hours after the evening meal Initial red blood cell count 1,010,000 per cu mm, hemoglobin 24 per cent (Sahli) The patient received 30 grams of an active preparation of desiccated stomach daily A maximum reticulocyte percentage of 13.5 was reached on the seventh day instead of the calculated 31.7 per cent The reticulocyte percentage returned to normal on the 11th day The red blood cell count reached 2,760,000 per cu mm in four weeks and 4,480,000 per cu mm in ten weeks

2 Man (No 243961), age 70 years Food from a meal 15 hours previously was found in the stomach on gastric analysis There was a history of similar findings during previous gastric examinations The initial red blood cell count was 2,610,000 per cu mm The patient was given 80 grams of desiccated stomach daily A maximum reticulocyte percentage of 6.8 was reached on the seventh day, although the calculated maximum percentage was 7.5 per cent, which should have been expected for less than one-half the dosage used In four weeks the red blood cell count rose to 3,280,000 per cu mm

The second phenomenon which suggests that some of the active substance may be generated after the stomach tissue is ingested, is the thermolabile character of the material as compared with the relatively more thermostable nature of the material in liver or liver extract While the dried stomach may be exposed for hours to temperatures of around 82 degrees C, in an atmosphere of petroleum benzene, without great loss of potency, in the presence of moisture, in 30 minutes at 60 degrees practically all the hemogenic activity is destroyed It is possible to extract some of the active principle from fresh stomach⁴³ or from Ven-

triculin⁴⁴ with water An acid aqueous extract (pH 4.5), evaporated at 82 degrees C proved to be ineffective in three patients who subsequently responded well to whole desiccated stomach An extract made by a method similar to that used in preparing liver extract, except that some of the protein was precipitated by a lead solution, showed but the faintest trace of activity (observed reticulocyte response 5.6 per cent, calculated 24.3 per cent) in a patient who subsequently responded perfectly to whole desiccated stomach tissue It is possible that the material was inactivated when heated to the temperature of 60 degrees C Meulengracht, et al,⁶ were unable to extract the active principle from stomach, using the methods reported by Cohn⁷ in the preparation of liver extract In interpreting these experiments it must be remembered, however, that the active principle may be destroyed more easily in the environment of the normal hog stomach tissue constituents (e.g., hydrochloric acid and pepsin present) than in the liver tissue, or may be more thermolabile

The next group of experiments throws light on the problem from another angle It was desired to study the hemopoietic activity of the various constituents of the stomach, to note whether one part was more active than another It was known from clinical experience that muscle tissue (meat) alone was not active in inducing a remission in pernicious anemia Sharp⁸ had postulated the theory that stomach tissue would be an active hemogenic agent because it had arisen from the same embryonic layer as the liver, al-

though Castle's¹ work has suggested a specific secretion from the stomach as an activating agent.

The mucosa and muscularis layers were carefully separated, dried and fed separately to patients with pernicious anemia. It was found that either layer was very effective in inducing the blood changes associated with a remission if the material was not heated. Thus 300 grams of fresh muscle layer dried to 64 grams caused a reticulocyte rise of 20.3 per cent (calculated rise 17.1 per cent) in a patient whose initial red blood cell count was 179 million per cu. mm. However, 30 gram doses (representing 230 grams of fresh muscle layer) for 10 days failed to cause a remission when the muscle tissue was dried, defatted with acetone and exposed to a maximum temperature of 65 to 82 degrees C. in the process. Similarly 64 grams of desiccated mucosa (representing 360 grams of fresh tissue) not exposed to heat, caused a maximum rise in the reticulocytes of 41.8 per cent in a patient whose expected rise was to 25.0 per cent. This confirmed the work of Wilkinson¹⁶ and explained our inability to obtain similar results in our original experiments² as the importance of the temperature factor was not appreciated at the time the first experiments were performed. The glandular portion of the mucosa, desiccated at a temperature of 65 to 82 degrees but not defatted, was fed in 30 and 60 gram doses daily (representing 158 and 316 grams of fresh mucosa) to another patient whose initial red blood cell count was 1,230,000 per cu. mm. With 30 grams daily there was a reticulocyte response to 6.8 per cent instead of the

expected 27.5 per cent. With 60 grams there was a secondary rise to 9.3 per cent. Subsequently this patient received whole stomach (28 grams of desiccated stomach representing 240 grams of the fresh organ) and had a very satisfactory increase of the reticulocytes to 36.6 per cent, in comparison to a calculated rise of 20.0 per cent. In four other patients who were fed this heated mucosa, three gave no reticulocyte response at all and one gave a questionable slight response.

It is of importance to recognize, however, that when the muscle layer and mucosa are ground together, and then exposed to the temperature of 65 to 82 degrees C. in the drying process, the hemopoietic activity is not destroyed. It is thought that an enzyme-like material is formed in the mucosa, and that it acts rapidly on the muscle layer at the death of the animal, so that by the time the two layers can be separated, some of the active material has been generated or has diffused through the tissues. The work of Castle suggests that this "enzyme" or generating substance is absent in the stomachs of patients with pernicious anemia. His evidence is that it is excreted by the stomach, and the present work shows that it originates from the glands of the mucosa.

VARIATIONS IN RETICULOCYTES DURING SHORT INTERVALS

Porter and Irving²⁰ have reported that following the administration of a potent aqueous extract of liver to patients with pernicious anemia there is a variation in the percentage of reticulocytes in as short an interval as a few hours. A study of the blood of twelve

patients (six treated with liver extract and six with desiccated stomach) was made at two to four hourly intervals to obtain additional information concerning this. It was found that in both groups there was considerable variation in the absolute numbers and percentages of reticulocytes during the course of the day. Variations up to a 168 per cent increase in two hours have been noted after desiccated stomach therapy and a 21 per cent increase in four hours after massive doses of liver extract. There was a tendency for the reticulocyte counts to be higher in the afternoon and evening than at other times during the day, but the incidence of the highest counts for all patients fell more frequently (31) during the sleeping hours (8 00 P M to 4 00 A M inclusive) than during the day (8 00 A M to 4 00 P.M inclusive).

Several factors enter into the prolongation or shortening of the three periods. Chronic infection prolongs the latent period, decreases the maximum percentage of reticulocytes and prolongs the period required for the return of the reticulocyte percentage to normal. The following case histories illustrate this condition.

EFFECT OF INFECTION

A patient (Case No 240147) with pernicious anemia had septic tonsils and chronic bronchitis. His initial red blood cell count was 1,120,000 per cu mm, hemoglobin 15% (Sahli) and leucocyte count 4800 per cu mm. He did not develop a leucocytosis at any time. His temperature during the first 27 days ranged between 99° F, and 102.5° F (37.5° C to 39° C) but was normal after the 28th day. The reticulocyte count reached a maximum of only 27.4% instead of 31.7% on the 17th day instead of the 7th or 8th day, and did not return to normal until the

29th day. However, in 62 days his red blood cell count reached 6,280,000 per cu mm and his hemoglobin 74% (Sahli), after taking 40 to 50 grams of dried stomach daily during the first 4 weeks and 20 grams daily thereafter.

Another patient (Case No 235661) with pernicious anemia and acute otitis media, had a temperature ranging from 99° F to 102° F (37.5° C to 38.9° C) during the first 17 days of treatment. During this time the maximum rise of the reticulocytes in response to the daily feeding with 40 grams of dried stomach, was 11.3% instead of the calculated 45.7%. On the 9th day of therapy he was given a blood transfusion. Following this there was a subsidence of the fever and improvement physically. The dried stomach was continued, and the reticulocyte percentage fluctuated from 6.2 to 11.8%. However, on the 10th day it reached a maximum of 19.5%, which was the calculated maximum for the new post-transfusion level of the red blood cells. Subsequently his red blood cell count rose to 5,310,000 per cu mm and his hemoglobin to 88% while taking 20 grams of the dried stomach daily. This patient did not show a leucocytosis during his infection.

Infection may cause a fall in the red blood cell count in spite of adequate therapy. Acute infection may not only prevent the rise in the reticulocyte percentage, but when once begun may cause its rapid fall. In a patient receiving liver extract, who developed erysipelas, it was noted that there was a rapid decrease in the number of reticulocytes (inhibition of production) and a failure of the red blood cell count to increase. After the infection there was a rapid recovery in the erythropoietic function.

Another circumstance which prolongs the three periods, and which prevents a maximum reticulocyte rise to its proper degree, is found when the therapeutic preparation is weak or

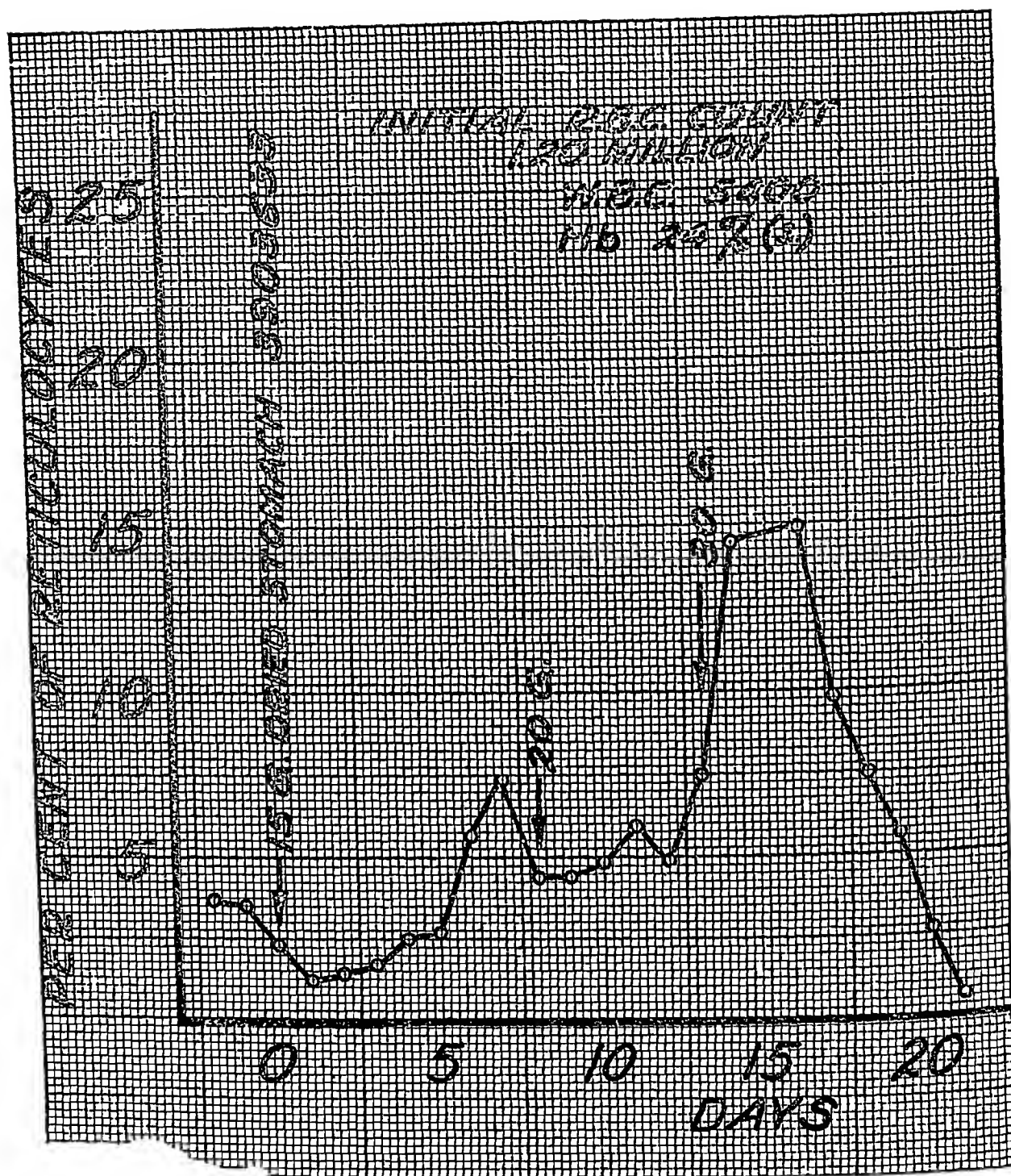


FIG 3 Shows the effect of suboptimal doses of an experimental preparation of dried stomach of a potency lower than normal 15 grams produced a definite effect but it was lower than one would expect 20 grams increased the effect and the maximum response followed the increase to 30 grams daily.

when the dose is insufficient The following figures show this condition in a patient receiving a non-defatted preparation of stomach of low therapeutic efficiency (Figure 3) and one receiving

liver extract of low potency. (Figure 4)

Figure 3 shows the increasing reticulocyte response in a patient fed increasing, but suboptimal amounts, of

a special stomach preparation of low therapeutic value Figure 4 shows the effects of two liver extracts of low therapeutic value, compared to the increase in the percentage of reticulocytes after a potent preparation

A dose above the maximum may shorten the normal four to five day period, after therapy has begun (Figures 5 and 6)

Patient No 241545, age 30 years The patient was given 50 grams of desiccated, defatted stomach on the first day, 150 grams the second day and 40 grams daily thereafter The "reticulocyte response" began within 24 hours, and was well established in 48 hours The maximum of 59.0% was reached on the 6th day (calculated maximum 45.7%) (Figure 5)

Patient No 194213, age 43 years The

patient was given 30 vials of Lilly's Liver Extract by stomach tube The "reticulocyte response" began within 48 hours, reaching a maximum of 55.7% on the 4th day (calculated maximum 45.7%) (Figure 6)

A submaximal reticulocyte rise due to a suboptimal dosage may be followed by a second reticulocyte rise if an optimal dose of an active preparation is given

Patient No 241529, man, age 59 years When first examined the patient had been taking 3 vials of Lilly's Liver Extract daily for 12 days He had an excellent subjective response, and on the 15th day his reticulocyte count had fallen to normal He was then given 30 grams of desiccated, defatted stomach daily A second "reticulocyte response" developed, reaching a maximum of 11.9% (calculated 20.4%)

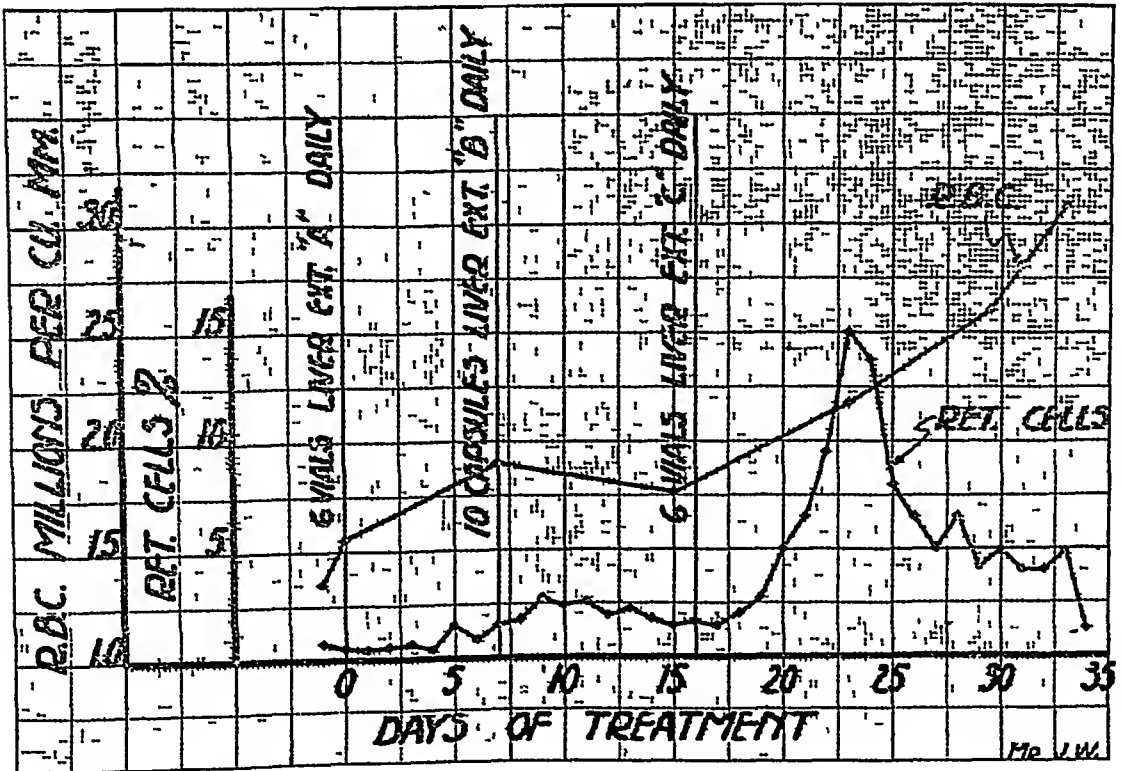


FIG 4 Shows the effect of three commercial liver extracts on a patient with pernicious anemia The first produced a delayed and inadequate response in increasing the percentage of reticulocytes, slightly accentuated by the second, but not at all comparable to the effect from the third (No 343, NNR)

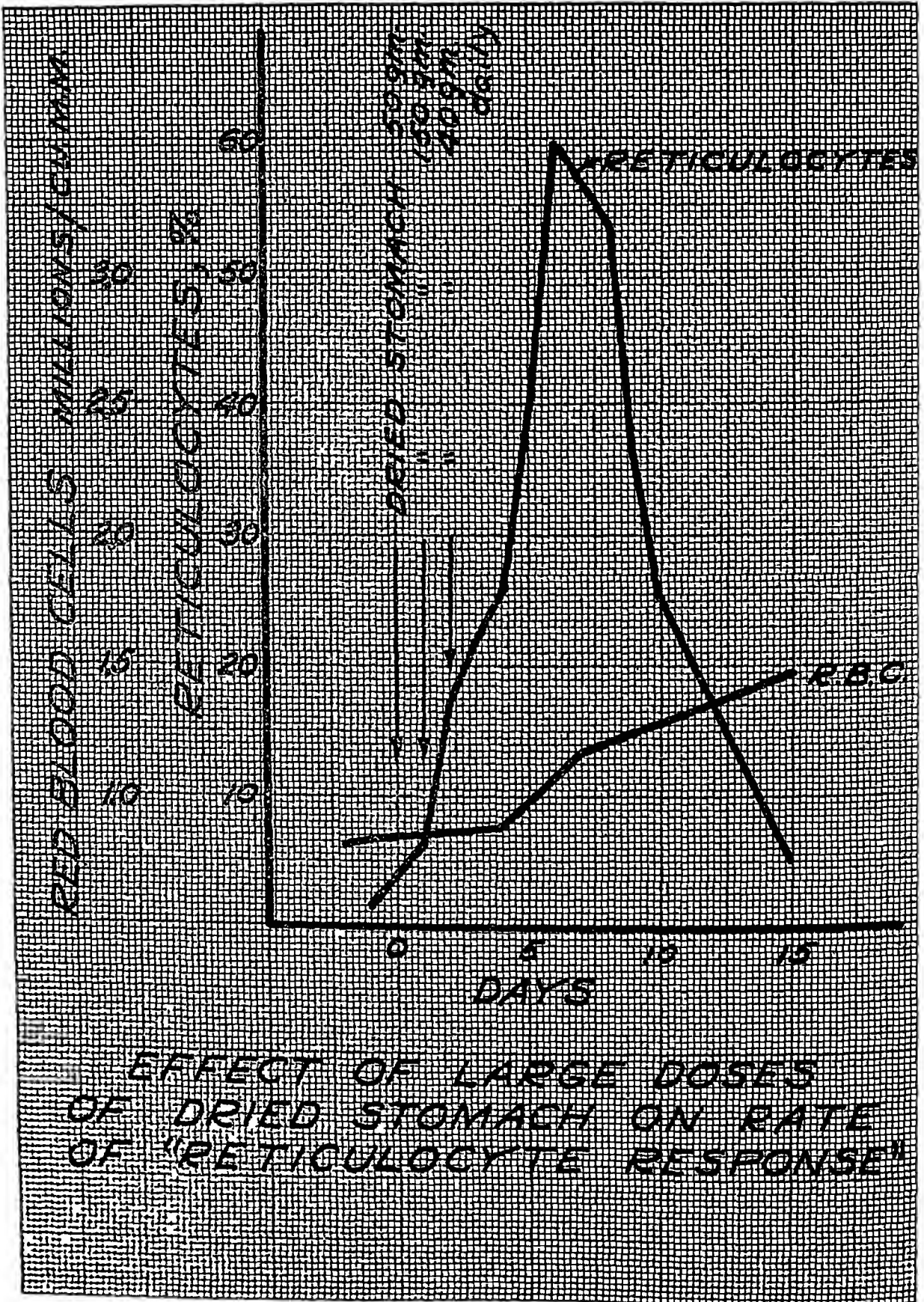


FIG 5 Shows the rapid and marked increase in the percentage of reticulocytes after massive doses of dried stomach, given by a stomach tube, to an irrational patient with pernicious anemia. The response started within 24 hours, instead of three to five days, and reached a very high maximum.

Patient No 227706, man, age 59 years. The patient took 3 vials of Lilly's Liver Extract daily for 21 days. At the end of this time the reticulocyte count had fallen to 7.1%, and reached normal during the next 3 days. He was then given 30 grams of desiccated, defatted stomach, and had a second "reticulocyte response" to 14.1% (calculated 38.0%)

The secondary rises in the percentage of reticulocytes are always below the calculated, the first rise having cleared out some of the immature cells of the bone marrow

EFFECT OF BLOOD TRANSFUSION

Three patients received blood transfusions at the beginning of their dried stomach therapy, because of unusual weakness, impending infections, or exhaustion. In two of these the rise in the percentage of reticulocytes was nearer to the calculated maximum for the new, post-transfusion level of the erythrocyte number, rather than to the original pre-transfusion count (Table III)

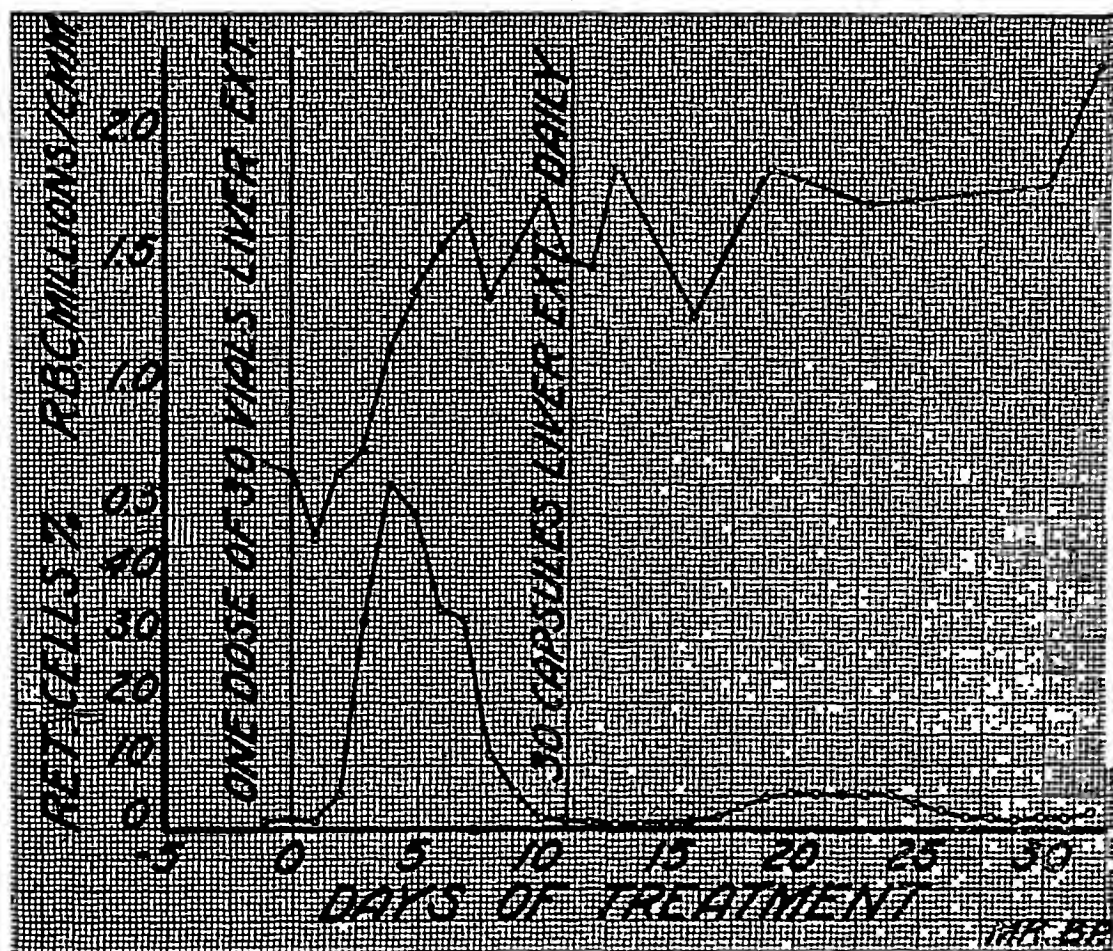


FIG 6 Shows the rapid response when a massive dose of liver extract was fed to a patient with pernicious anemia. The reticulocyte increase began with 48 hours, instead of from three to five days.

TABLE III

Patient	Initial RBC Count Millions per cu mm	Expected Maximum Reticulocyte per cent	Post Transfusion RBC Count Millions per cu mm	Maximum Reticulocyte per cent.	
				Expected	Actual
241074	0.89	38.0	1.34	26.5	35.1
162296	0.69	45.7	1.21	29.0	33.5
235661	0.75	41.6	1.63	20.4	19.5

CHANGES IN THE RED BLOOD CELL COUNT

In a group of 46 of the 50 patients of whom complete data was available, the following chart shows the average increase in red blood cell count per week after adequate doses of desiccated stomach

400,000 per week. Individual patients reaching red blood cell counts of four million per cu mm or more showed increases of 994,000, 637,000 and 580,000 per week. The rate of increase was not equal during all months following the beginning of the treatment, being slower after the first month and

TABLE IV

Week	Number of Observations	Average Red Blood Cell Count Millions per cu mm	Week	Number of Observations	Average Red Blood Cell Count Millions per cu mm
0	46	1.72	7	10	4.14
1	45	1.73	8	18	4.34
2	39	2.34	9	6	4.60
3	23	2.57	10	4	4.40
4	13	3.26	11	4	4.82
5	20	3.34			
6	10	3.61			

It will be noted that during the first week of therapy there was practically no increase in the average number of red blood cells per cubic millimeter. In individual cases there was a slight increase and in others an actual decrease in number. The first significant rise is generally noted after two weeks. After the first week there is an average increase, for all the patients, of

comparatively very slow after the second month. Figure 7 shows the monthly changes for 46 patients, compared with those of 90 patients treated with liver diet, and reported by Minot and Murphy.⁹ The average rate of increase in the two is substantially the same, being slightly more rapid in the stomach treated cases than in this liver treated group.

RELATION OF SIZE OF DOSE AND RATE OF CELL DEVELOPMENT

There appears to be a definite correlation between the size of the dose of desiccated stomach and the time required for the red blood cell count to reach four million or more per cubic millimeter. Seven patients receiving from 100 to 199 grams per day (in terms of fresh tissue) required on the average 52.4 days to reach four million red blood cells per cu mm. Ten patients receiving 200 to 249 grams per day required 40.1 days to reach the same level (Figure 8). Of 25 patients with initial red blood cell counts of 0.9 to 2.8 million per cu mm, no patient with uncomplicated pernicious

anemia required more than 35 days to reach the four million level if he received more than the equivalent of 230 grams of fresh stomach, and no patient reached four million in 35 days unless he received 180 grams or more. Eleven patients in this group received from 186 to 215 grams of stomach (in terms of the fresh material) and required from 28 to 63 days to reach four million red blood cells per cu mm, regardless of the initial count. The following table shows a comparison of the average number of days to reach the four million level when liver extract or when desiccated stomach was used. This does not take into account the varying dosage.

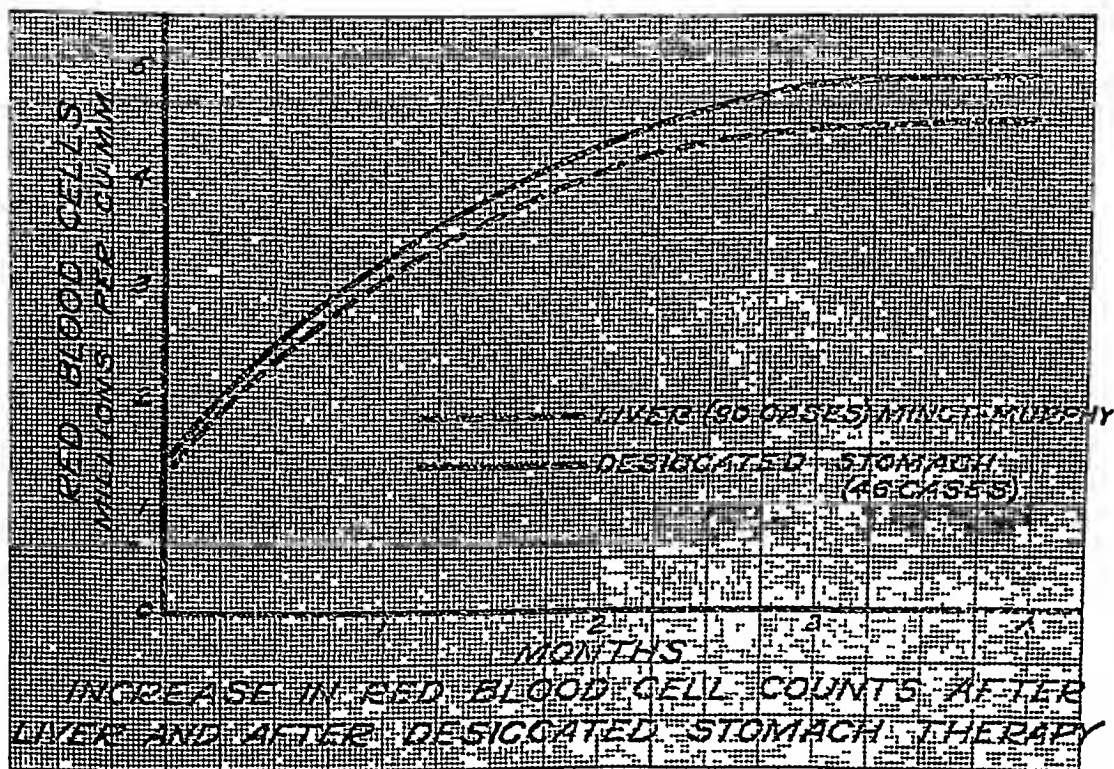


FIG 7 Shows the average increase, by months, in the red blood cell counts of pernicious anemia patients treated with whole liver and with desiccated stomach. The upper line (stomach) shows a slightly more rapid rise when compared with the lower (liver), although the difference is probably not significant.

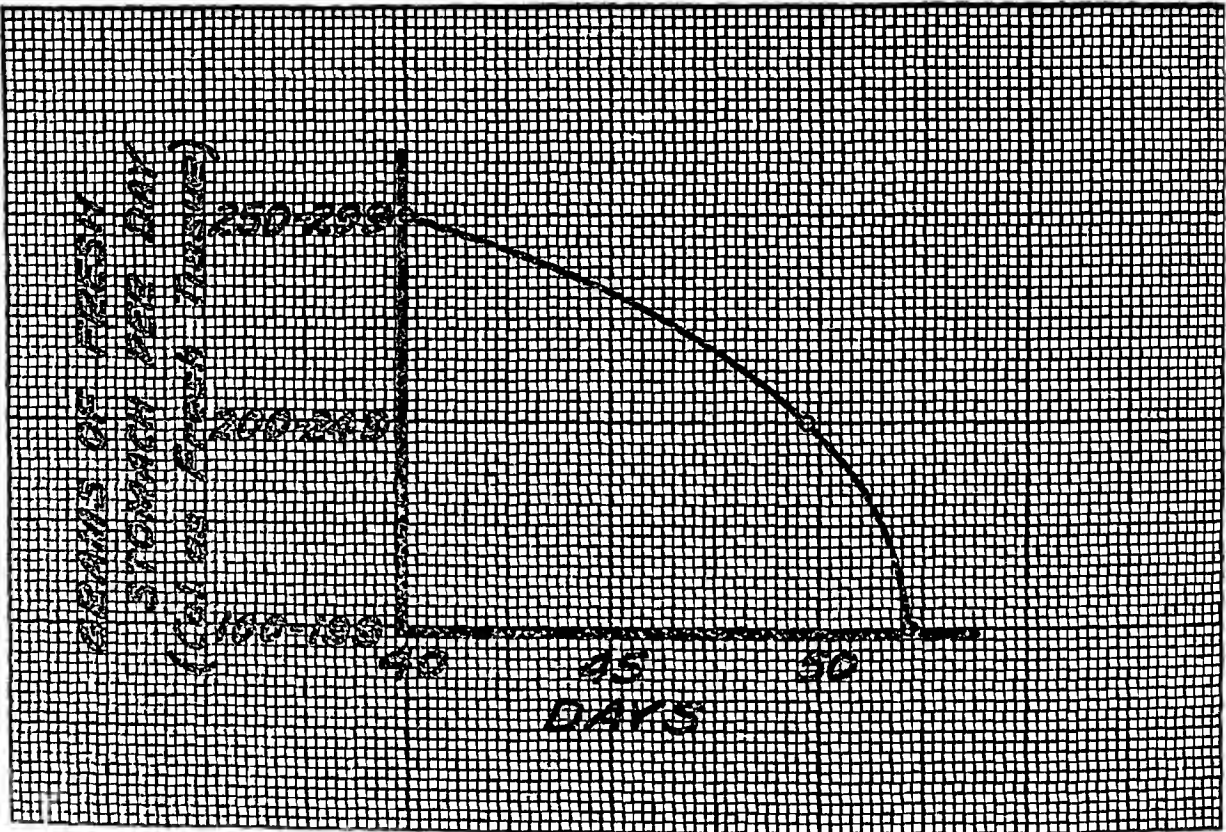


FIG 8 Shows the average increase in the rapidity of the improvement of the red blood cell count when larger doses of desiccated stomach are fed, in comparison to smaller doses

TABLE V

R.B.C (Millions)	Number Patients	Liver Extract	Number Patients	Dried Stomach
0-0.9	7	56.9 days	2	51.5 days
1.0-1.9	17	38.6 days	14	47.9 days
2.0-2.9	9	34.9 days	9	43.0 days

It is thus evident that within the dosage group classified as "adequate" it takes, on the average, comparatively longer for the patients with red blood cell counts below one million per cu mm. to reach normal, than for those having a higher initial count. In both the stomach and liver treated groups it required but four to five days longer, on the average, for the 1.0 to 1.9 group than the 2.0 to 2.9 group to reach the four million level.

WHITE BLOOD CELLS AND PLATELETS

With the onset of the remission, there is a gradual increase in the number of white blood cells and platelets¹⁸. There appears to be no gross difference between the response after liver extract and after stomach therapy. Eosinophilia has been reported after raw liver diet, but no definite eosinophile increase has appeared after desiccated stomach therapy in the blood of 30 patients examined daily during the first 30 days, and at intervals during six to twelve months afterwards¹⁹.

RATE OF UTILIZATION, EXCRETION OR DESTRUCTION: RELAPSES

Riddle and Sturgis¹⁰ showed that 30 vials of liver extract given in one dose had the same effect as three vials of

liver extract given daily for ten days Kandel²¹ also reported a case in which 240 grams of Ventriculin given in four days were effective for eleven days. The material is evidently stored in the body, and not excreted or destroyed at once. It is suggestive that when the material is made by gastric digestion in a normal person, it is stored, possibly in the liver, as this organ appears to have such a rich content of the material. The storage of the active material may be the mechanism by which a remission is maintained after the cessation of stomach or liver therapy. The length of a remission, when therapy is discontinued, varies with each patient. The relapse is apparently more rapid when no medication is taken than when a subminimal dose is used. Of 35 relapses in 33 patients which relapsed because of discontinuance of therapy, or too small dosage or non-potent material, records are on hand of three patients on stomach therapy and 32 on liver or liver extract therapy. The relapses, as indicated by a decrease in the red blood cell count, appeared in from ten days to nine months. The average period for the development of a complete blood relapse is probably slightly less than two months, and appears to be essentially the same in patients treated with liver extract or with stomach, although the series is at present too small to permit the drawing of definite conclusions. In the three relapses in patients treated with stomach, the blood count decrease was noted in from two to two and one-half months after a normal blood count, during which period the medication had been discontinued or an insufficient amount taken. The most rapid relapse after

liver extract therapy was noted in a patient in whom the red blood cell count fell from 5,060,000 per cu mm to 2,300,000 in ten days. There is evidently rapid destruction or counteraction of the hemopoietic substance during infection.

PATIENTS APPARENTLY REFRACTORY TO LIVER, RESPONDING TO DRIED STOMACH

Occasionally a patient is encountered who does not respond perfectly to liver, and the blood count cannot be increased appreciably above three million per cubic millimeter. The following case history illustrates this point.

A man (Case No 210673), age 65 years, gave a history of pernicious anemia of at least 3 years duration. When liver extract, 6 vials daily, (343, NNR) was begun his red blood cell count was 1,250,000 per cu mm, and his hemoglobin 25% (Sahl). He had a typical "reticulocyte response" and in 23 days his red blood cell count was 3,400,000 per cu mm and his hemoglobin 65% (Sahl). He was given 4 vials of a liver extract daily after this, but no change was noted in the blood count in 36 days. It was thought that the particular liver extract used was not of normal potency, so the dose was doubled (8 vials daily). No change occurred in 21 days and the liver extract was changed to a lot of known potency, 4 vials (343, NNR) daily. There was a slight drop in the red blood cell count in 30 days, it was unchanged in 35 more days of this therapy, and again the same after 34 more days, and 26 days and 63 days. Thus the blood count remained around 3 million for 245 days using what was usually an adequate dose of a potent liver extract. The patient was then given 14 grams of dried, defatted stomach daily, the dose being reduced to 10 grams later. The blood count taken 8 weeks later showed a slight increase to 3,870,000 red blood cells per cu mm., and 83% hemoglobin (Sahl), with great subjective improvement. The count rose

rapidly to 4,390,000 per cu mm and the hemoglobin to 91% (Sahli) where it has remained for 3½ months to the present

Renshaw,¹¹ Leschke,²³ and Snapper and Dupreez¹² reported similar cases.

EFFECT OF LIVER EXTRACT, LIVER OR DESICCATED STOMACH ON SECONDARY ANEMIAS

Sixteen patients with various types of anemia were treated with liver or liver extract and three with desiccated stomach. In only two was there a therapeutic response attributable to the medication. One, a patient with fish tape worm infestation and anemia, responded well to whole liver and the other, a patient with myxedema and anemia, responded to liver extract. While either liver or stomach therapy appears to be specific for the macrocytic anemias of the pernicious anemia type, including sprue (Castellani,¹⁸) it is possible that empirically other conditions may be found which may be helped.

CAUSES OF FAILURE IN THE TREATMENT OF PERNICIOUS ANEMIA WITH DESICCATED STOMACH OR LIVER EXTRACT

Our experience seems to have demonstrated clearly that the blood of a patient with uncomplicated pernicious anemia will return to normal following the administration of adequate doses of desiccated hog's stomach^{2, 3}. Proof of this is to be found in treating our own series of 100 patients and confirmatory evidence is available in the published results of Conner,¹⁴ Wilkinson,¹⁵ Renshaw,¹¹ Snapper and Dupreez,¹² Rose now,¹⁶ Meulengracht and Hecht-Johansen,⁶ Hitzenberger¹⁷ and others²¹⁻⁴⁷.

When the treatment is applied to some patients, however, the anticipated improvement may not follow. This situation requires the careful consideration of several possible explanations as follows:

- 1 The diagnosis of pernicious anemia may be incorrect. As far as it is known at present, desiccated stomach is effective only in pernicious anemia and sprue.¹³ Assuming that it has an action similar to liver or liver extract, it may be surmised that it will also benefit patients with the so-called "pernicious anemia" of pregnancy, and the anemia associated with *Dibothryocephalus latus* infestation. There are other varieties of anemia which resemble the pernicious type and yet do not respond to stomach therapy. Probably one of the most confusing is aleukemic leukemia, which in some instances is differentiated from pernicious anemia only with the greatest difficulty. All other types of anemia which do not respond to the modern treatment of pernicious anemia must be eliminated before it can be said that the therapy is ineffective.

- 2 It is known that any type of acute infection with a febrile reaction reduces, to a certain extent, the effectiveness of desiccated stomach. If the treatment fails, therefore, an attempt should be made to eradicate all forms of active infection. If this cannot be eliminated, the dose should be doubled and every effort made to minimize the effect of the counteracting agent.

- 3 Occasionally failure is due to the fact that the patient is not under constant observation and takes only a small portion of the prescribed dose. Too often efficient therapy is discarded be-

cause the red blood cell count is said not to increase during the first week or two of treatment. While it is true that the average red blood cell count increases between 400,000 and 500,000 per cu mm per week, this increase is not always in the form of a smooth curve for each patient. As shown in an earlier section, in some there is no change for a week or two, and then a rapid rise at the rate of a million or more cells per cu mm per week. It should be emphasized, furthermore, that the earliest change which is noted in the blood is not necessarily a rise in the red blood cell count but an increase in the reticulocytes. It should also be emphasized that the number of reticulocytes which appear following treatment is inversely proportional to the initial red blood cell count before treatment, and that they do not show as an increased percentage in the peripheral blood when the red blood cell count is three million or more.

4 If the above possible explanations can be eliminated, it must be concluded that the preparation used is not potent. This possibility may be eliminated if the preparation which has been used is known to have been subjected to a clinical test by responsible observers and certified as active. The preparation of defatted, desiccated hog stomach is not a complicated procedure, and the possibility of destroying the potency of the material during the manufacturing process should not be great. But, as the active material in the substance is not identified, its exact stability to heat and various changes of pH are not known, and very slight alterations in these may readily impair

or completely destroy the potency of the preparation.

PRACTICAL MANAGEMENT OF PATIENTS WITH PERNICIOUS ANEMIA

The essential part of the treatment is to be assured that the patient receives a sufficient amount of potent material which is effective in the treatment of pernicious anemia. If desiccated stomach (Ventriculin) is used, a safe daily dosage is ten grams for each million deficit in the red blood cell count. For example, if the red blood cell count is one million, there is a deficit of four million, and the dosage should be 40 grams daily, when the level of the red blood cell reaches two million, the deficit is three million, and the dosage should be 30 grams daily. After the blood becomes normal it is necessary for the patient to continue with a maintenance dose for an indefinite period in order to prevent a relapse, which will occur at a variable period after the medication is discontinued. The precise dosage per week which is necessary to prevent a recurrence of the anemia is not definitely known at present, and it is possible that it varies with different patients. An average dosage is ten grams a day for five or six days a week. When the dosage has been reduced to ten grams daily, the only safe plan is to have the patient report at intervals of every two or three weeks for a blood examination. If the red blood cell count remains at a normal level for over two months, it may be concluded that the dosage is adequate, but if there is a decrease, a larger dosage is indicated. From our experience we have con-

cluded that the most accurate single criterion of the adequacy of the dosage is the level of the red blood cells, and this should be determined at each time the patient returns for examination. Although the red blood cell count may increase to more than five million per cu mm, there is no evidence that it will reach an abnormally high level if an excess of medication is given. The fear, therefore, that a polycythemia may develop is unwarranted.

The accessory methods of treatment depend upon the symptoms. A patient with anemia should remain at rest in bed for the first week or two of the treatment if the red blood cell count is extremely low. It has been our practice, however, to urge patients to become ambulatory at the earliest possible moment but to avoid excessive fatigue. The diet should be liberal and well balanced, but otherwise requires no special attention. With a few exceptions, the choice of food may be left to the patient as the increased appetite which develops with the treatment usually calls for a wide variety of food in large amounts. There is no convincing evidence that it is necessary to administer dilute hydrochloric acid, despite the fact that patients with pernicious anemia have an achlorhydria and free hydrochloric acid never returns in the gastric contents after the blood becomes normal. In the series of patients whom we have treated about one-half were given dilute hydrochloric acid in doses of 4 c.c., *t i d*, or more, and the others received no medication except liver, liver extract or desiccated stomach. The results in both groups were equally good and there was no apparent difference in the rate of re-

covery from the anemia or the rapidity with which the gastro-intestinal symptoms disappeared. As the effect of the modern method of treatment is so prompt and satisfactory, it does not seem necessary to employ the therapeutic agents such as iron and arsenic, and they have not been used in the patients whom we have observed.

For the prevention of bed sores, reddened areas may be coated at frequent intervals with a collodion solution. When the bed sores are large, necrotic tissue may be cut away and wet dressings of boric acid can be applied. When the edges become clean, the wound may be exposed to the air, or to the light and heat from an ordinary carbon filament electric light bulb.

IMPORTANCE OF COMPLICATING INFECTIONS

As previously emphasized, an acute infection of any type, if it is associated with fever, causes the action of liver or desiccated stomach to be less effective. The infection which is most frequently encountered is one involving the urinary tract, and usually consists of a cystitis alone or a cystitis associated with a pyelitis. This arises in patients with spinal cord changes, which result in urinary retention due to loss of control of the sphincter of the urinary bladder. Any other type of infection, such as acute tonsillitis, sinusitis, bronchitis, bronchopneumonia, acute cholecystitis, or erysipelas may produce the same deleterious effect. It is doubtful if various foci, such as chronic and mild infection about the teeth, are of importance in this connection, and, therefore, their removal

should be recommended only after it has been demonstrated conclusively that efficient stomach therapy is not producing satisfactory results. In the presence of an acute complicating infection with fever, every method to combat it should be employed, and in addition the dose of desiccated stomach should be increased from 50 to 100 per cent.

BLOOD TRANSFUSION

It is rarely necessary to resort to this procedure as most patients react promptly to liver or stomach therapy. It is useful, however, as an emergency measure, and should always be considered when the patient's condition is serious or if red blood cell count is one million per cu mm or less. It has been our practice to determine the blood group of all patients whose red blood cell count is one million or less, and to have a donor available for use if it appears that the patient may die before the usual therapy has time to act. Some patients with an extremely low red blood cell count are delirious and uncooperative when first seen, which makes impossible the administration of any medication by mouth. As there is no effective preparation of liver or stomach, commercially available which can be administered subcutaneously or intravenously, and the injection per rectum is only moderately efficient, the medication must be given by means of a stomach tube. Excellent results may be obtained by employing a tube with semi-rigid walls and administering 100 grams or more of desiccated stomach which has been mixed with a sufficient quantity of water to insure that it will pass through the tube readily. Al-

though a portion of this may be vomited, a sufficient quantity will be retained to produce an effect, and more may be given at intervals of three or four hours.

DISCUSSION

The fact that desiccated, defatted, hog's stomach is effective in the treatment of pernicious anemia is of importance from a practical as well as a theoretical standpoint. There is no evidence that this preparation is more effective than liver in the treatment of this disease, although our observations are compatible with the conclusion that fresh stomach tissue contains, or develops, the active substance in a more concentrated form than fresh liver. It is possible, however, that this is not the case, as a fairly large amount of the active principle in liver may be destroyed or lost in the process of manufacture of liver extract. As the preparation of desiccated stomach is relatively simple and the original tissue employed is ordinarily regarded as a waste material, the cost of the finished product should be less than liver extract. When it is considered that a patient with pernicious anemia must consume a certain amount of effective material constantly in order to maintain health, this is an important item for consideration. Most of the patients do not find the material difficult to consume, and some prefer it to liver extract. At present liver extract has the advantage of being soluble in water, whereas the desiccated stomach does not dissolve.

Certain theoretical considerations as to the nature of the development and method of action of the blood-maturing substance offer opportunity for

speculation. The blood-maturing substance appears to be present in liver tissue as a definite material and it can be extracted and concentrated. The potency of the whole stomach suggests, then, that the material is developed post mortem in the tissues. A generating substance, then, may exist in one layer (the mucosa) which acts on the proteins of the other layer (muscularis). It is possible that the generating substance is of the nature of an enzyme, and it is apparently excreted in normal gastric juice. The fact that the material can be made in the stomach during gastric digestion, and is present in liver and other tissues, leads one to conclude that it may be made and stored by the body. This probably accounts for the latent period of development of anemia when liver or desiccated stomach tissue therapy is discontinued. The desiccated stomach may have a supply of the active substance which it has generated while drying, or additional substance may be made after it has been ingested. Meulengracht and Hecht-Johansen⁶ suggest that this is the case, as they were unable to extract it by the method of Cohn used in making liver extract. However, it may be that the material is destroyed by this process, although it hardly seems possible that it should be stable in liver tissue and not in stomach tissue.

The fate of the substance is not known. The quantitative relationship between the size of the dose and the rate of response, and the relapse when the dose is below a certain minimum, suggests that a certain definite amount of the material is used. More of the active substance is required and used

when the peripheral blood count is low than when it is high. Three vials of Lilly's Liver Extract or ten grams of desiccated stomach (Ventriculin) daily, supply sufficient material when the red blood cell count is four and one-half to five million per cu. mm, but the response is very slow if this dosage is given when the cells number one million or less per cu. mm.

There are several possible ways in which the active material may act:

1. *Replacement Theory*. The active material may supply a missing substance directly and cause a normal development of the blood.

2. *Hormone Theory*: It may stimulate other organs, or tissues, to produce an adequate amount of a hemogenic substance, or change the rate of growth of the bone marrow cells directly.

3. *Defective Metabolism Theory*. It may act as an intermediate substance which, after undergoing further metabolic changes, becomes part of the developing red blood cells.

4. *Antitoxin Theory*. The material may neutralize an inhibiting substance.

The lessened activity of the active substance as the blood count approaches normal, as evidenced by the decreased production of reticulocytes and the slower rate of increase of the red blood cell count during the later weeks and months after the beginning of therapy, suggests that the material has a specific action on the stages of the red blood cell which are most numerous during the relapse, the megaloblast and normoblast. It is possible that the increase in the number of white blood cells with the onset of the remission is a mechanical incident, associated with the release of large num-

bers of cells from the crowded, hyperplastic bone marrow. This is somewhat substantiated by the absence of improvement in the leukemias after liver extract or desiccated stomach therapy.

SUMMARY AND CONCLUSIONS

1 Defatted, chopped, desiccated whole stomach (hog) is effective in inducing and maintaining a hemopoietic remission in pernicious anemia.

2 A comparison has been made in the clinical progress and laboratory data of 50 patients treated with Lilly's Liver Extract (No 343, N N R) and 50 patients treated with desiccated, defatted stomach (Ventriculin, N N R).

3 The defective maturation of immature red blood cells in the bone marrow of patients with pernicious anemia appears to be related to the lack of an enzyme-like substance developed in the gastric mucosa.

4 The material made by the mucosa, produces from protein a substance which stimulates red blood cell maturation.

5 The material may be produced post-mortem when the mucosa and muscle layer are ground together.

6 The subjective and objective changes in both groups (liver treated and stomach treated) are alike.

7 As with liver extract, the maximum reticulocyte count is inversely proportional to the initial red blood cell count, after desiccated stomach therapy. The anticipated maximum reticulocyte count may be estimated with a remarkable degree of accuracy.

8 The reticulocyte count may vary during the course of the day from one

or two per cent to 16.8 or 21.0 per cent, in two to four hour intervals. The greatest increase in the reticulocyte percentage came most frequently during the hours of sleep at night, in the cases studied.

9 The response to the therapy may be lessened or inhibited in the presence of infection or if the preparation is weak or the dose insufficient.

10. The latent period before the development of the reticulocyte increase may be shortened by a massive dose of liver extract or desiccated stomach.

11. A submaximal reticulocyte rise, due to a suboptimal dosage, may be followed by a second reticulocyte rise if an optimal dose of a second preparation is given.

12 The reticulocyte response may be submaximal in patients who have gastric retention.

13 A decrease in the maximum reticulocyte percentage following desiccated stomach therapy has been noted after blood transfusion.

14. The average length of time for 50 patients treated with Ventriculin to reach the maximum reticulocyte percentage was 7.52 days, whereas for the liver group it was 6.9 days. The difference is attributed to the greater solubility of the liver extract, with more rapid absorption.

15 The average maximum reticulocyte percentage of the liver treated group was 22.36 per cent (calculated 23.43 per cent) while that for the stomach treated group was 24.19 per cent (calculated 19.61 per cent).

16 During the first week or two of therapy the increase in the number of

red blood cells may be negligible, but after that there is an average increase of about 400,000 per week, more rapid during the early weeks and slower as the five million level is reached

17 Within the limits of adequate dosage, the larger the dose of desiccated stomach, the shorter the time required to reach a normal red blood cell count.

18 With the development of the remission, the number of leucocytes and blood platelets approaches normal.

19 No eosinophilia has been noted after stomach therapy, as after raw liver therapy

20 The active material in liver extract or desiccated stomach may be stored in the body, the supply or effect being adequate for a variable pe-

riod, but is rapidly counteracted or neutralized by infection.

21 Causes of failure of liver extract or desiccated stomach therapy are incorrect diagnosis, infection, insufficient dosage, or deficient potency of the preparation

22. The optimal daily dosage of desiccated stomach is ten grams (equivalent to about 67 to 70 grams of fresh stomach) for each one million deficit in the red blood cell count.

23. Active infection must be eliminated and in its presence the dose of desiccated stomach or liver extract must be increased.

24. Blood transfusion may be indicated in selected cases with extremely low blood counts, debility or acute infection.

BIBLIOGRAPHY

- ¹CASTLE, W B and LOCKE, E A Observations on the etiologic relationship of achylia gastrica to pernicious anemia Jr Clin Invest 1928 vi, 3-4.
- CASTLE, W B, TOWNSEND, W C, and HEATH, C W Etiological relationship of achylia gastrica to pernicious anemia Lancet, 1930, i, 1062-3
- CASTLE, W B Observations on the etiologic relationship of achylia gastrica to pernicious anemia I The effect of the administration to patients with pernicious anemia of the contents of the normal human stomach recovered after the ingestion of beef muscle, Am Jr Med Sci, 1929, clxxviii, 748-764
- CASTLE, W B, and TOWNSEND, W C Observations on the etiologic relationship of achylia gastrica to pernicious anemia II The effect of the administration to patients with pernicious anemia of beef muscle after incubation with normal human gastric juice, Am Jr Med Sci, 1929, clxxviii, 764-777
- ²STURGIS, CYRUS C, and ISAACS, R Desiccated stomach in the treatment of pernicious anemia, Jr Am Med Assoc, 1929, xciii, 747-749
- ³ISAACS, R, and STURGIS, CYRUS C. Some newer remedies in the treatment of pernicious anemia, desiccated stomach, Jr Am Med. Assoc, 1930, xcv, 585-587
- ⁴MINOT, G R, COHN, E. J, MURPHY, W. P, and LAWSON, H A Treatment of pernicious anemia with liver extract; Effects upon the production of immature and mature red blood cells, Am. Jr Med Sci, 1928, clxxv, 599
- ⁵RIDDLE, M C. Blood regeneration in pernicious anemia during early remission, Arch Int Med, 1930, xli, 417-439
- ⁶MEULENGRACHT, E, and HECHT-JOHANSEN, A Behandlung der Perniziösen Anämie mit Magen und Magenextrakt, Klin. Wchnschr, 1930, ix, 1162-1165
- Ugesk f Laeger, 1930, xcii, 405-409

- ⁷COHN, E J, MINOT, G R, ALLES, G A, and SALTER, W T The nature of the material in liver effective in pernicious anemia, *Jr Biol Chem*, 1928, lxxvii, 325-358
- ⁸SHARP, E A An antianemic factor in desiccated stomach, *Jr Am Med Assoc*, 1929, xciii, 749
- ⁹MINOT, G R, and MURPHY, W P A diet rich in liver in the treatment of pernicious anemia, *Jr Am Med Assoc*, 1927, lxxxix, 759-768
- ¹⁰RIDDLE, M C, and STURGIS, CYRUS, C The effect of single massive doses of liver extract on patients with pernicious anemia, *Am Jr Med Sci*, 1930, clxxx, I-II
- ¹¹RENSHAW, A Treatment of pernicious anemia with desiccated hog's stomach, *Brit Med Jr*, 1930, i, 334-335
- ¹²SNAPPER, I, and DUPREEZ, J D G Behandeling von perniciose anaemie met Poeder von Gedroogde Varkensmagen, *Nederlandsch Tijdschrift voor Geneeskunde*, 1930, lxxiv, 745-747 *Nederlandsch Tijdschrift voor Geneeskunde*, 1931, lxxv, 29-48
- ¹³CASTELLANI, A Brief notes on the administration of liver, pancreas and stomach extracts in sprue, *Jr Trop Med and Hyg*, 1930, xxxiii, 126
- ¹⁴CONNER, H M The treatment of pernicious anemia with raw and cooked swine stomach, *Jr Am Med Assoc*, 1930, xciv, 388-390 *Jr Am Med Assoc*, 1931, xcvi, 500
- ¹⁵WILKINSON, J F Pernicious anemia, preliminary report on the results obtained by treatment with certain preparations of stomach, *Brit Med Jr*, 1930, i, 236-239
- ¹⁶ROSENOW, G Behandlung der perniziösen Anämie mit getrocknetem Schweinemagen, *Klin Wchnschr*, Berl, 1930, ix, 652-653
- ¹⁷HITZENBERGER Case report, *Proc Gesellschaft f inn Med in Wien*, *Wien klin Wchnschr*, 1930, ix, 293
- ¹⁸NITTS, SAVAS Blood platelets in pernicious anemia after liver therapy, *Ann Int Med*, 1931, iv, 931-938
- ¹⁹GOLDHAMER, S M Non-development of eosinophilia in pernicious anemia patients treated with desiccated stomach, *Ann Int Med*, 1931, iv, 1105-1107
- ²⁰PORTER, WM B, and IRVING, HAZELWOOD Reticulocytosis produced by liver extract, *Arch Int Med*, 1929, xlv, 502-503
- ²¹KANDEL, ERNESTINE Ventriculin in the treatment of pernicious anemia patients on meat free diet, *Proc Soc Exp Biol and Med*, 1931, xxviii, 385-389
- ²²GEUTING, H Treatment of pernicious anemia with stomopson, *Deutsch med Wchnschr*, 1930, lvi, 1219-1220
- ²³LESCHKE, E Die magentherapie leberrefraktärer Fälle von perniziösen Anämie, *Med Klin*, Berl, 1930, xxvi, 1445-1446
- ²⁴DECASTELLO, A Erfahrungen über die Behandlung der perniziösen Anämie mit dem Magenpräparat Ventramon, *Med Klin*, Berl, 1930, xxvi, 1444-1445
- ²⁵BERTRAM, F Klinisches zur Behandlung der Anämien mit Magenpräparaten, *Klin Wchnschr*, Berl, 1930, ix, 2103
- ²⁶HENNING, N, and STIEGER, G Die Behandlung der perniziösen Anämie mit Magenschleimhautpräparaten, *Klin Wchnschr*, 1930, ix, 2145
- ²⁷BAUER, R, and WOZASEK, O Influence of ergotamine and of liver diet on functioning of liver, *Wien klin Wchnschr*, 1930, xliii, 1337
- ²⁸FABER, K Die Behandlung der perniziösen Anämie mit getrockneter Magensubstanz, *Ugeskrift f Laeger*, Copenhagen, 1930, xcii, 467-468
- ²⁹WINGE, K Pernicious anemia, treatment with desiccated stomach, *Ugeskrift f Laeger*, Copenhagen, 1930, xcii, 511
- ³⁰TORRNING, K Pernicious anemia treated with dried stomach, case, *Ugesk f. Laeger*, Copenhagen, 1930, xcii, 510
- ³¹HOLBOLL, S A Treatment of pernicious anemia with dried stomach, *Hospitalstidende*, Copenhagen, 1930, lxxii, 825
- ³²UNGLEY, C C The stomach and pernicious anemia, *Newcastle Medical Journal*, 1929, x, 14-39
- ³³LENHARTZ, H Ersetzt Organsubstanz aus Schweinemagen die Leber bei Be-

- handlung der Biermerchen Krankheit?
Deutsch med Wchnschr 1930, lvi,
1872-1873
- ³⁴DOMINGUEZ, C, and BIZZOZERO, R C
Sindrome neuro-anemico; Tratamiento
por la ingestion de e stomago de cerdo
desecado, El Dia Medico, 1930, iii, 49
- ³⁵GUTZERT, K Über die Behandlung des
Morbus Biermer mit Magenpulver
(Ventraemon), Munch med Wchnschr,
1930, lxxvii, 1625-1626
- ³⁶ALLERTON, G T Desiccated hog stom-
ach in pernicious anemia, Lancet, 1930,
ii, 795
- ³⁷GODEL, R Behandlung der perniziösen
Anämie mit Ventraemon (Magen-
preparat), Wien klin Wchnschr, 1930,
xliii, 812-814
- ³⁸HERZ, A Therapie der Anämien, Wien.
klin Wchnschr, 1930, xliii, 1189-1194
- ³⁹BURGESS, J P, and MORGAN, J E · Ef-
fect of various stomach preparations in
pernicious anemia, Proc Soc Exp
Biol and Med, 1931, xxviii, 371-372.
- ⁴⁰LAMBIN, P, and STEENHOUDT, J Essai
de traitement de l'anemie pernicieuse
par des preparations d'estomac desseche,
Bull et Mem de la Soc. Méd des
Hôp de Par, 1930, xlv, 986-991
- ⁴¹JAGIC, N, und KLIMA, R Zur Therapie
der perniziösen Anämie mit Ventraemon,
Wien klin Wchnschr, 1930, xliii, 877-
878
- ⁴²MOUZON, J Stomach therapy in per-
nicious anemia, Presse méd, 1930,
xxxviii, 847-850
- ⁴³Unpublished observations of the authors
- ⁴⁴Personal communication from Dr R M
McKean and Dr E A Sharp Paper
in press.

The Adequate Treatment of Anemia*†

By GEORGE R. MINOT, M.D., S.D., F.A.C.P.,** and WILLIAM B. CASTLE, M.D., F.A.C.P.,*** *Boston, Massachusetts*

INTRODUCTION

THE adequate treatment of anemia necessitates removal of the causes, whether proximate or remote, with attention to all aspects of a given case. The dependence to a greater or less degree of many cases of anemia upon an inadequate nutrition of the individual either produced directly by defects of the diet, or indirectly conditioned by a defect of the individual, makes the study of this aspect of the problem of primary importance. For this reason, it is our object not to discuss the use of special procedures such as transfusion of blood or splenectomy, but to emphasize the importance of a suitable diet and the use of optimal quantities of certain

potent substances contained in food and shown to work almost as specifics for certain types of anemia. Adequate treatment, however, implies that the individual peculiarities of each patient and of his condition must be considered.

PERNICIOUS ANEMIA

The adequate treatment of pernicious anemia is accomplished not by liver, kidney, stomach, brain, or potent preparations obtained from these organs, but by *enough* potent material, irrespective of the source, for the given individual throughout life. Successful treatment demands that the physician should know that the patient actually takes the amount prescribed. Sometimes the patient believes that he has been taking the proper amount, but after the physician inquires carefully, he discovers that the individual frequently omits a dose or has undoubtedly taken an insufficient amount. Confusion can arise from the fact that the amount of liver purchased will not be the amount of liver ingested. The amount prescribed should be the quantity to be swallowed. In preparing raw liver pulp or cooking liver, frequently from 20 to 35 per cent of the tissue is lost. Doctors and patients often believe that if

*From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital, and the Department of Medicine, Harvard Medical School.

†Read at the Baltimore Meeting of the American College of Physicians, March 27, 1931.

**Professor of Medicine, Harvard Medical School, and Director of Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital.

***Assistant Professor of Medicine, Harvard Medical School, and Associate Physician, Thorndike Memorial Laboratory, Boston City Hospital.

the patient takes extract derived from 100 grams of an organ, he will obtain as much potent material as if he ingested 100 grams of the organ itself. Such is certainly not the case. Often the amount of extract derived from 100 grams of liver will be about as potent as 65 grams of prepared liver. The physician should know the potency of the preparation advised. He may obtain for himself such information by observations on the course taken by the reticulocytes or by referring to critical studies published by other persons. It is usually a relatively simple matter to initiate a remission in pernicious anemia by the daily feeding of various substances such as 200 to 300 grams of prepared liver or kidney, active extracts derived from 300 to 600 grams of liver, 150 or 240 grams of fresh whole pig stomach, or stomach mucosa or dried and defatted stomach prepared from this amount. Brain (Ungley) is about one-third as potent as liver. Failures will be found to be due to inadequate dosage, incorrect diagnosis or complications. Occasionally, unusually large doses are necessary, particularly because of complications and also sometimes owing to difficulty with absorption. When no response or a poor response has occurred with a known potent preparation, the amount should at least be doubled. In the case of a very sick patient, the entire dose of potent material for a week may be given within a few hours or even administered at one time to an unconscious patient by stomach tube. In this way the appearance of the response will be hastened.

Sometimes it is necessary to consider administering a potent preparation parenterally. Occasionally this method may be live-saving or be more convenient, and, under certain circumstances, it may have distinct advantages.[†]

The dose of potent material necessary for the maintenance of a normal red blood cell count and hemoglobin level and for the relief or prevention of progress of symptoms varies widely; in terms of liver extract* daily from that amount derived from 200 grams to that derived from 1200 grams of liver. The red blood cell count and hemoglobin alone should not determine the dose. These factors, considered together with the color index, the detailed character of the red cells (their size, volume index, etc.,) and white blood cells and blood platelets, and particularly the patient's signs and symptoms, should determine whether more, or rarely less, potent material should be taken. The object should be to make all aspects of the patient's blood normal and the patient himself as well as possible. The size of the cells can be fully as important a guide to dosage as the red blood cell count, but the patient's symptoms, especially if referable to the central nervous system, are as important as any laboratory examination in considering the amount of liver or potent substitute the individual should take. If a simi-

[†]See Castle, W. B. and Taylor, F. H. L., *Intravenous Use of Extract of Liver*. Jr. Amer. Med. Assoc., 1931, xcvi, (April 11), 1198, and papers by these authors on *Intramuscular Use of Liver Extract*, in press for Jr. Amer. Med. Assoc.

*Liver extract No. 343 Lilly (N. N. R.)

lar group of patients are compared, who have been relieved of severe anemia and who have had no definite subsequent relapse, (a condition always attributable to an *insufficient* amount of active principle or to complications,) it will be found that the patients who maintain the best health are usually the ones who take daily distinctly large amounts of potent material. It is important to adhere to the principle of supplying optimal quantities of effective substances to maintain the 'best possible' health rather than to supply only enough to maintain definite improvement. The prescription of a proper amount of potent substance demands a knowledge of conditions that may inhibit its action. Infections, disorders of the liver, kidney, and other organs can hinder the effects of liver and potent substitutes. The usual adequate dose may need to be increased because of age or arteriosclerosis. In fact, for old people with arteriosclerosis, it usually will require at least double the amount of active principle to maintain health that is needed for individuals without complications below the age of 45 years. An increased amount of potent material is indicated when neurological symptoms cease to lessen and of course when neurological complications tend to show further progress. Many patients under liver treatment have had lesions referable to the neuro-muscular system develop or increase because they did not take enough potent material for their individual needs.

The treatment of the lesions of the nervous system seems best carried out by feeding with regularity large

amounts of potent material—not merely the amount that will maintain a normal blood level. Whether the effect on the blood and the nervous system is due to one or more substances is open to speculation. Organs contain many substances not in extracts used for therapy and the latter in turn contain various materials, such as vitamin B₂ (G) in concentration, besides the substance crystallized by West and his associates, which is potent for blood regeneration in pernicious anemia. Possibly neuro-muscular symptoms may be affected more favorably by the feeding of organs than by extracts of equivalent potency for blood regeneration. Neuro-muscular symptoms often do not significantly change until the red blood cells have reached normal numbers and then may lessen very slowly. Since there is almost always some decrease in neurological symptoms with persistent large doses, the necessity of persevering with maximal amounts of active material is clear. If arteriosclerosis or complications are not present and especially if the nervous system lesions are of relatively recent origin or referable to the peripheral nerves, large amounts of liver or potent substitute will usually cause relatively rapidly pronounced improvement in the nervous manifestations. One can not expect, with long-standing advanced lesions of the central nervous system, great improvement in older people, but even in such cases, very large amounts of potent material over a prolonged period of time can be distinctly beneficial.

In carrying out adequate treatment, all aspects of the patient and his case

must be prescribed for. Care should be taken of the gastrointestinal tract and every effort made to obtain complete absorption of potent products. Appropriate, skillfully applied mechano-therapeutic procedures, mental hygiene, and many other sorts of matters must be wisely attended to. Certain restrictions often must be prescribed. One that has not been mentioned in the literature but which has been noted by Dr West of New York, as well as by Dr Murphy and ourselves, is that perhaps it is unwise for these patients to expose themselves to the sun sufficiently to tan their bodies intensively. Under such conditions it is possible that neurological manifestations have been distinctly aggravated and caused to progress with great rapidity.

Lack of attention to the diet may be a cause for a patient with pernicious anemia not to improve as much as possible. At times undesirable low color indices may occur when the red blood cell count is normal. Occasionally this state of affairs can be attributed to diets which for a long period of time have been scant in protein, vegetables and fruit. Under such conditions when the patient is taking ample extract of liver, the addition of iron may cause the hemoglobin to rise. The prescription of a proper diet is also obviously desirable. Sometimes, when the red blood cell count is about 4,000,000 per cu mm. and hemoglobin about 70 per cent, both the red blood cell count and the hemoglobin can not be increased by large doses of potent substances effective in pernicious anemia. In some such cases, especially if pronounced arteriosclerosis or obvious

complications are not present, iron in sufficient dosage will cause a distinct improvement not only in the blood but in the patient's sense of well-being.

If chronic blood loss is sufficient to cause anemia in a patient with pernicious anemia who has maintained a normal blood level with an adequate amount of potent material, he may develop hypochromic anemia which can be readily lessened by iron therapy*.

Other substances than iron, as well as food, may operate to improve the blood of pernicious anemia patients when they are in a state of remission. For example in rare instances hypothyroidism and pernicious anemia may be present in the same individual. The relief of anemia may not be completely possible without the administration of a potent thyroid preparation in addition to adequate therapy for pernicious anemia.

Frequently, after the patient appears to have improved as much as possible as a result of taking for months, not weeks, distinctly large quantities of potent material, the physician is confronted with this question which the patient more often asks before a month has passed by, "How much less medicine can I now take?" The answer is always difficult. It is safe, when the amount has been distinctly large, to curtail the dose somewhat. One should be prepared to return to large doses again on relatively slight provocations. It is unwise, however, for any patient with pernicious anemia to

*A chart illustrating this state of affairs for one of our cases is given in an article by R. T. Beebe and G. E. Lewis in the *Am. Jr. Med. Sci.*, 1931; clxxxix (June), 796.

take daily less than 200 grams of prepared liver or the amount of potent material equivalent to that contained in the most potent commercial extracts derived from 300 grams of liver.

An occasional patient with pernicious anemia may remain, as before the days of liver therapy, in a state of splendid remission without any particular treatment for a year and even more, but this in no way contraindicates the important principle for the patient with pernicious anemia to understand—namely, the necessity of continuing to take indefinitely and with regularity the quantity of potent material optimal for the given case

Rarely cases with a blood picture of pernicious anemia occur with normal amounts of free hydrochloric acid in the gastric contents. Some such cases have arisen as the result of partial removal of the stomach or disorders of the lower intestinal tract, and some are cases of sprue. The principles of treatment are no different under these circumstances, just as it is unnecessary to administer hydrochloric acid to the case of pernicious anemia with gastric achlorhydria. This is because Castle has shown that individuals may have a normal gastric acidity yet lack the factor which is absent from the stomach in all pernicious anemia patients, who almost always have achlorhydria. This factor, which occurs in the normal stomach, when brought in contact with beefsteak, liberates a substance that is effective in pernicious anemia. It is likewise pointed out here that achlorhydria often occurs in patients

with idiopathic hypochromic anemia, but their gastric secretions contain the gastric factor lacking in pernicious anemia. One should recognize that it is not achlorhydria that conditions the state of pernicious anemia, but the lack of a particular factor secreted by the normal stomach which is not hydrochloric acid, pepsin, rennin, or lipase.

ANEMIAS THAT RESPOND TO IRON

The principles of the adequate treatment of anemias that can respond to iron are essentially the same as those set forth for pernicious anemia. Iron may have pronounced favorable effects on blood regeneration. The many conflicting statements in the literature concerning the value of iron therapy are probably dependent upon deductions from circumstances that were not the same. Iron may control important activities within cells, it influences growth and thus affects the body metabolism besides supplying this element for hemoglobin formation. The course taken by the reticulocytes will foretell, if properly evaluated, the effectiveness of iron therapy in a given case. The character of the curve for the reticulocytes in response to iron is somewhat different from that which appears with liver therapy in pernicious anemia. Likewise data concerning the reticulocyte increase from iron administration must be interpreted slightly differently than those for pernicious anemia.

There are various sorts of so-called "secondary" anemias that can be promptly alleviated by the use of iron in suitable doses. Anemia due to

chronic blood loss usually lessens rapidly under iron therapy. Patients with "secondary" anemia dependent upon either no well-recognized cause or associated with certain dietary deficiencies or altered gastrointestinal function, or both, are among those benefited often by iron. Such cases are common in women and the anemia may be enhanced by blood loss, pregnancy, infection, and other complications. The condition known as chronic chlorosis or hypochromic achlorhydric anemia is distinctly one in which the patient is favorably affected by large doses of iron. The rôle played by the disturbed gastric function is unknown but, indeed, may be most important.

Infections and various complications or conditions inhibit the action of iron comparable to the effect of such disorders on the treatment of pernicious anemia, so that brilliant results from iron therapy can not be expected in anemia of infectious origin. Likewise iron cannot influence aplastic or myelophthisic bone marrows or be definitely effective when a distinct degree of abnormal blood destruction continues to be operative as in chronic hemolytic jaundice.

The principle of giving enough iron to accomplish the best possible result must be adhered to. Often small doses of iron (75 mgs.) in the form of an iron salt such as ferrous carbonate, iron citrate, or iron and ammonium citrate or reduced iron may cause a rise of reticulocytes and slow improvement of the patient, when larger doses (0.5 gram) will produce brilliant and rapid results. Sometimes, especially in chronic chlorosis, a daily

dose of 75 mgs. of iron *per se* contained in a salt will produce no effect whatsoever, when 350 mgs. of iron will cause pronounced benefit. Although iron is apparently more effective when absorbed from an acid than from an alkaline medium in the upper gastrointestinal tract, if sufficient iron is given the ultimate benefit observed will be the same. Many papers have appeared concerning whether one sort of iron preparation is more effective than another. Although much more knowledge concerning this subject and the physiology of iron metabolism is desirable, it would seem that the form in which iron is prescribed is less important than that it is in sufficiently large quantities and in such a state that it can be readily absorbed. For this reason it would seem wise to give a salt of iron preferably already dissolved. Metallic iron may need solution by the body and pills or capsules containing iron compounds may pass through the gastrointestinal tract intact. Iron and ammonium citrate is a readily soluble inexpensive salt which may be given dissolved in milk. Because of the occasional diarrhea, induced by the large doses necessary, it is well to begin with a dose of about half a gram three times a day and increase to the generally useful dosage of two grams three times a day.

It is probably unwise to stop iron therapy as soon as the blood has returned to normal in a case that can be considered truly curable as, for instance, a case of chronic blood loss with the blood loss stopped. Presumably at the time the number of red blood cells and hemoglobin have

reached normal, the body is still deficient in iron, so that it is desirable for the patient to continue taking iron for at least some weeks after the blood appears to be completely regenerated. Moreover, there are undoubtedly cases of chronic chlorosis and somewhat similar cases with relatively higher color indices, in which the cause of the anemia is not clear-cut, that will inevitably relapse unless iron therapy is continued indefinitely. It is such cases that may have a defect in the utilization of iron, dependent in some way on abnormal gastrointestinal function comparable perhaps to the defect in gastric secretion that occurs in pernicious anemia. Adequate treatment of this type of patient demands frequent observations and the insistence of iron therapy presumably throughout the life of the patient. Omission of iron may cause relapse in from a few weeks to months or sometimes not for several years. Some data at hand suggest that after iron is omitted a relapse will occur sooner in the patients who have taken iron for a short rather than a long period of time.

Although iron alone can be very effective, there are other factors that can accelerate blood formation in anemias influenced by iron. Copper, under certain circumstances, probably especially in infants, as Josephs has shown, may enhance the blood-regenerating power of iron. Hart and his associates first demonstrated this effect in young rats with anemia produced by the feeding of a whole milk diet. The iron salts commonly prescribed for patients usually have copper in small amounts mixed with them and perhaps some of the effects cred-

ited to large doses of iron should be attributed to the synergetic action of copper and iron.

Liver contains many substances other than the active principle effective in pernicious anemia. The commercial extracts prepared particularly to supply the latter substance are effective in certain other megaloblastic anemias resembling typical Addisonian pernicious anemia. They are occasionally effective in severe anemias not suspected to be associated with a megaloblastic bone marrow. Usually these extracts are not significantly effective in "secondary" anemia and undoubtedly many patients have wasted money and effort in buying and taking such products that can not be expected to benefit them. Whole liver, in the large amounts effective for pernicious anemia, may have a remedial effect in many cases that can be benefited with iron. This effect is certainly not attributable only to the iron contained in liver. Whipple and his associates have shown that liver contains, in addition to iron, material effective in the promotion of hemoglobin regeneration in anemia due to chronic blood loss in dogs. They have isolated a fraction of liver potent in this respect that is distinct from the fraction effective for pernicious anemia. In their animals, supplementing this liver fraction with small amounts of whole liver may increase the total output of hemoglobin above the level due to the liver fraction alone. Whipple has also shown in his dogs, and we have observed in the clinic, that liver extract for pernicious anemia is essentially inert in anemia due to chronic blood loss, but upon supplementing it with a relative-

ly little whole liver, the effect in the dogs and in an occasional human case is greater than the influence of either alone. Clinical observations show that large amounts of liver can be effective in the regeneration of blood following chronic blood loss and in some other cases of "secondary" anemia, but that it is usually less potent and far less easy to take than iron salts. Sometimes liver will have little or no effect on anemias of ill-defined origin in which iron will produce rapid blood regeneration. The addition of liver, however, to the diet of a patient improving with iron can act sometimes to accelerate blood regeneration, especially as the hemoglobin approaches the normal level

Iron apparently acts to produce blood regeneration by an effect additional to supplying the element for hemoglobin formation. It alone can not supply the loss from the body of material valuable for hemoglobin formation, but liver and kidney particularly, as well as other foods, contain material necessary for new hemoglobin fabrication. Although iron alone can often produce, with a satisfactory diet, excellent results, it is to be recognized that liver or potent substitutes with iron may cause maximal blood regeneration. If treatment with iron and liver, or a suitable substitute, is prescribed because the combination offers the greatest chance for the greatest improvement in anemic patients, some patients will take material that is unnecessary, and knowledge regarding the effectiveness and action of substances will not be obtained. Sometimes one can demonstrate clearly the influence of different materials by

feeding for periods of time first one and then another substance.

We have seen cases that were certainly not ones of pernicious anemia, with the red blood cells about 2,000,000 per cu.mm and the color index close to one, that responded to liver extract effective in pernicious anemia with rapid regeneration of the red blood cells to normal, but with only slight increase of the hemoglobin over a period of weeks. At that stage, however, iron caused rapid regeneration of hemoglobin. Cases also have been observed that were inert to alcohol precipitated liver extract, but in which whole liver slowly produced regeneration of the red cells to normal with some rise of hemoglobin. In these cases, upon the addition of iron, there followed a rapid rise of hemoglobin to normal. When iron alone is given the hemoglobin and the red blood cells often increase rapidly to normal. Sometimes the red blood cells rise quickly, for example from 3,000,000 to 4,500,000 per cu mm and the hemoglobin from 40 to 70 per cent. Without further treatment than iron and a satisfactory diet there may then be a very sluggish rise of the hemoglobin and red cells, but sometimes in such cases if whole liver is added, the hemoglobin rapidly rises to normal and the red blood cells promptly increase still further. It is thus desirable to learn the effect of different factors on blood regeneration in not only various sorts of anemias, but in anemias due to the same cause under varying conditions. Important conditions that may vary are the degree of anemia, the character of the red blood cells, the amount of reserve

supplies of blood-building materials in the body, the secretions of the stomach, and other states of the gastrointestinal tract

THE IMPORTANCE OF DIET

The diet of each patient with anemia must be carefully considered and individually prescribed, or adequate treatment will not be given. The relationship between diet and anemia was mentioned in the 17th century. Although the scientific foundations for the value of food for patients with anemia were laid by Menghini in 1746 and by Verdel in 1849 when they showed by feeding animals food rich in iron that this element could be increased in their blood, it is only within recent years that the importance of diet in causing or alleviating anemia has been broadly recognized. Even so, knowledge concerning the influence on blood formation of different sorts of food or substances they contain is in its infancy and there is need for a wider appreciation of the fact that anemia often can be wholly or partially related to the partaking of an unsuitable diet for a period of years.

A carefully obtained and detailed history concerning the patient's dietary habits throughout life often will suggest a reason for anemia and can lead to the selection of a desirable diet for a given case. The part played by chronic digestive disorders, such as colitis with diarrhea and achlorhydria with or without other altered physiological mechanisms in preventing the absorption or utilization of factors necessary for blood formation is always for evaluation. Temporary gross dietary deficiencies do not pro-

duce significant symptoms but departure from an optimal diet, even if slight, can produce ill health when operative over a long period of time and especially if combined with digestive disturbances. For example, it is common to observe women who eat little or no breakfast, a lunch composed chiefly of concentrated carbohydrate foods and a fairly satisfactory evening meal who have slight anemia and often constipation. In such cases, without other cause for the anemia than improper food, an ordinary well-balanced diet rich in fruits and green vegetables and containing ample animal protein not only can correct the anemia, but improve much more the patient's general sense of well being. Iron or liver or both may accelerate the improvement.

In known chronic vitamin deficiencies in man anemia is a symptom. The anemia may be dependent upon other factors than the lack of a given vitamin, but at times as in chronic scurvy in adults it can be related directly to the lack of vitamin C. In such instances iron and liver extract potent for pernicious anemia are not effective, but food rich in vitamin C can produce a reticulocyte response and rapidly lessen the anemia. Anemia can also arise from long-standing deficiency of protein and lessen when ample protein food is supplied.

These examples of ill-defined and distinct dietary defects simply hint at the many varieties of defective diets that can play a rôle in the production of anemia. In such conditions as well as in others, food alone, excluding liver or potent substitutes, can restore the blood to normal, although often in

such cases, iron with or without liver is necessary for effective or rapid results. In anemia, however, the body is probably often depleted in the products needed to build cells and hemoglobin; such occurs, for example, in chronic blood loss and in long-standing dysentery as well as when the food intake has been obviously chronically deficient in one or more respects. Iron and liver extracts indeed may produce great benefit, but in order to establish a completely normal state of affairs, other elements are required for the manufacture of blood which can be supplied by food for optimal nutrition. For example, we have demonstrated that patients with anemia from prolonged chronic blood loss treated with iron regenerate their blood more slowly when their diet is composed of crackers and milk than when it contains muscle meat, vegetables, and fruits.

It is only desired to indicate here that the greatest improvement in the anemic patient will be obtained when, in addition to distinctive therapy, attention is paid to the diet. The patient's weight, age, and state of his digestive system must be considered in prescribing the diet. Simply because diarrhea exists, the diet must not be abnormal in quality. In certain vitamin deficiencies, looseness of the bowels may be a result and the prolonged diarrhea may increase the cause. In such cases, the physical state of the food may need modification; but the diet should contain optimal quantities of food for the best possible nutrition. Certain foods may delay the digestion of other foods or upset the digestive functions; for ex-

ample, fat, except in small amounts in the diet of many pernicious anemia patients, often disturbs the digestive process as well as leads to an undesirable gain of body weight. One must not only consider for a given anemic individual the selection of food from the point of view of furnishing ample blood-building materials and supplying food for optimal nutrition, but also take into account the preparation of the food and the exact dishes to be served.

THE IMPORTANCE OF ATTENTION TO EVERY PHASE OF EACH CASE

Large amounts of whole liver, together with big doses of iron and an adequate well-balanced diet offer the greatest chance of improvement to the anemic individual. Such treatment, however, is of a "shot gun" nature and will not determine the exact importance and action of different factors. Treatment given routinely in this manner will tend to lead to neglect of all the aspects of the patient's case. Every phase of each case must be properly considered and treated and the patient, a human being himself, must never be neglected.

An example of where attention to the patient's conduct of life and his diet had a profound effect on his sense of well-being is as follows.

A man of 60 years of age with pernicious anemia in a state of remission for two years had taken regularly sufficient liver extract to maintain his red blood cells at about 47 million per cumm and hemoglobin at 80 per cent. He had suffered for the last eight months of this time from weakness, fatigue, various symptoms referable to an unstable vaso-motor system, considerable intestinal flatulence and

mental depression. Numbness in his hands developed, but varied greatly from hour to hour in its intensity. He had eaten an excess of sugar and concentrated starch food and it was believed that he had an intestinal carbohydrate indigestion. He, also, was confronted with anxiety regarding his children and had lost much sleep. Furthermore, he had discussed the symptoms of pernicious anemia with other individuals who suffered from this disease and believed he had a rapidly progressive disorder of his spinal cord. Prolonged optimistic talks with the patient, curtailment of the carbohydrate in his diet, regular moderate exercise and longer hours in bed at night, without change in the daily dose of liver extract caused within a few weeks pronounced improvement in his health. The numbness in his hands disappeared, the gastrointestinal tract functioned properly and his strength returned and co-

incidentally the hemoglobin increased over ten per cent and the red blood cells about 400,000 per cu mm.

In the future, more will be learned about the relation of the gastrointestinal tract to anemia and to other chronic disorders. Also knowledge will be broadened concerning the rôle that diet and substances contained in food play in the etiology and treatment of anemia. This will be accomplished from observations at the bedside expanded in the laboratory by not only trained clinical investigators, but by all practitioners of medicine. This is one of the most important ways that knowledge is obtained that leads to the alleviation of suffering and the prevention of disease.

Complement Fixation in the Diagnosis of Amebiasis*†

By CHARLES F. CRAIG, M A , M D., F A C P , Colonel, Medical Corps, U S. Army, *Washington, D.C*

BY the term "amebiasis" is meant the condition brought about in the human body by the invasion of the tissues of the intestines by *Endamoeba histolytica*, the ameba causing that type of dysentery called "amebic dysentery" Most unfortunately, from the standpoint of a clear understanding of the importance of this parasite as a cause of disease in man, the term "amebic dysentery" has, until quite recently, been synonymous with "amebiasis" in the minds of the vast majority of the medical profession In addition, the conception that infection with *Endamoeba histolytica* occurs only in the tropics and sub-tropics has led the profession far astray regarding the real importance of this parasite to human medicine throughout the world

As the result of many surveys by competent investigators, of all classes of people in many temperate regions, as well as in the tropics and sub-tropics, we know that *Endamoeba histolytica* is world wide in distribu-

tion and that, so far as the United States is concerned, from five to ten per cent of individuals harbor this parasite The percentage is far higher in some parts of our country, while it is somewhat lower in others, but a conservative estimate places the infection of the general population of the United States at about five to ten per cent. Fortunately, most of the individuals infected do not show marked symptoms of their infection, but clinical observations of infected individuals have shown that from 20 to 50 percent do have symptoms, and that in most such individuals proper treatment resulting in the elimination of the parasite, also results in the disappearance of the symptoms.

As long ago as 1891, Dock¹ demonstrated that amebiasis is not a tropical disease, and that amebic lesions of the intestine could be present in persons free from dysentery and with no history of the infection. The observations of Dock were confirmed in 1910 by Musgrave², who demonstrated at autopsy that marked ulceration of the intestine may occur even though no recognizable symptoms are noted, and it is well known that abscess of the liver may occur in individuals with no

*From the Department of Preventive Medicine and Clinical Pathology, Army Medical School, Washington, D C

†Read at the Baltimore Meeting of the American College of Physicians, March 25, 1931

history of diarrhea or dysentery. In 1921, I⁸ called attention to the atypical symptoms often present in individuals infected with *Endamoeba histolytica*, symptoms having little in common with the classical symptom-complex known as "amebic dysentery", and to the great importance of regarding the latter condition as the most severe result brought about by the invasion of the intestine by this parasite.

Within recent times, an immense amount of evidence has accumulated demonstrating that marked deviations from health may be produced by this parasite without dysentery ever occurring and it may be truly stated that for one case of amebic dysentery there are hundreds of cases of amebic diarrhea or other conditions due to the parasite. In those individuals showing no symptoms of the infection we must believe that an equilibrium has been established between the host and the parasite, and that the damage done by the parasite is repaired immediately. However, this resistance to the parasite may be broken down in various ways, so that the recognition of the infection and the elimination of the parasite is important, even in these more fortunate individuals.

Whether *Endamoeba histolytica* can live in the lumen of the human intestine without invading the tissues is a question now being carefully investigated, but personally, it is believed that in every individual harboring this parasite some injury to the tissues is produced, and that the amount of this injury directly influences the character of the symptoms present, or their absence. If comparatively few

amebae are invading the tissues of the intestine, symptoms may be entirely absent, the minute lesions produced by the amebae healing promptly, while, if larger numbers invade the intestinal walls, the symptoms may vary from those characteristic of mild invasion to those recognized as typical of the symptom-complex known as "amebic dysentery". The important fact to be borne in mind, from the recent studies of this infection, is that *Endamoeba histolytica* is world wide in distribution and is the cause of much invalidism hitherto unrecognized as being due to this parasite. As Lynch⁴ says "We have come, then, from knowing amebic dysentery as the disease produced by *Endamoeba histolytica*, to the point where this is recognized as the uncommon acute, or relatively acute, phase of the disease, while there exists in the population at large an incidence of latent infection conservatively estimated at from five to ten per cent, in many, if not all, of which it is the belief of careful and competent experienced men that there is a chronic low-grade disease of devitalizing quality but diagnosable only on finding the amebae."

The recognition of these latent infections with *Endamoeba histolytica* is most important and, at the present time, rests upon the demonstration of the parasite in the feces of the infected individual. When the services of a competent protozoologist, or of one trained in the study of the various species of amebae occurring in the intestine of man (of which there are no less than five species) is available,

TABLE I
Illustrating the time of Disappearance of the Complement Fixation Reaction
for *Endamoeba histolytica* after Treatment

Case No	Date of Examination	Complement Fixation Test for <i>E. histolytica</i>	Feces Examination for <i>E. histolytica</i>	Date Examined After Treatment	Complement Fixation Test for <i>E. histolytica</i>	Feces Examination for <i>E. histolytica</i>	Days after Cessation of Treatment
1.	July 17	+ + + + +	Positive	Aug 27	—	Negative	21
2	Aug 2	+ + + + +	Positive	Sept 25	—	Negative	30
3	Dec. 29	+ + + + +	Positive	Jan 31	—	Negative	18
4	Jan 12	+ + + + +	Positive	Jan 31	+ +	Negative	5
5	July 6	+ + + + +	Positive	Sept 17	—	Negative	21
6	July 23	+ + + + +	Positive	Sept 9	—	Negative	28
7	Dec. 27	+ + + + +	Positive	Jan 23 Feb 6 May 22	+ + + + + — + + + + +	Negative Negative Positive (re-lapse)	14 20 130
8	July 23	+ + + + +	Positive	Oct 25	—	Negative	60
9	Jan 16	+ + + + +	Positive	Feb 12	—	Negative	14
10	Mar. 20	+ + + + +	Positive	May 15 June 10	— —	Negative Negative	21 46
11	Feb 27	+ + + + +	Positive	June 10 Nov 11	— —	Negative Negative	56 206
12	June 19	+ + + + +	Positive	July 7	—	Negative	3
13	July 31	+ + + + +	Positive	Aug 29	—	Negative	7
14	Sept 11	+ + + + +	Positive	Oct 16	—	Negative	12
15	Sept 16	+ + + + +	Positive	Oct 18	—	Negative	11
16	Oct 2	+ + + + +	Positive	Nov. 6	—	Negative	14
17	Nov 20	+ + + + +	Positive	Jan 15	—	Negative	14
18	Sept 6	+ + + + +	Positive	Sept 28	—	Negative	6

NOTE. In two of the cases cited the Wassermann and Kahn tests gave four plus reactions and these remained so after the disappearance of the positive reaction for infection with *Endamoeba histolytica*

the diagnosis can be made, but there is great difficulty in differentiating the various amebae of the human intestine and such a differentiation can be made only by one with training and experience. *Endamoeba histolytica* is the only pathogenic ameba occurring in the intestine and hence has to be differentiated from the four other species of ameba that occur there, for a diagnosis of amebiasis based merely upon finding an ameba in the feces is absolutely worthless. The development of some method of diagnosis which would eliminate, if possible, the necessity of differentiating the amebae, would obviously simplify the problem, and it has been with the hope of doing this that I have endeavored to apply the principle of complement fixation to the diagnosis of amebiasis. It has been found possible to do this and in previous publications^{5,6,7} I have described such a test and the results obtained with it.

As regards the technique it may be stated briefly that it follows the standard method for the complement fixation test for syphilis used in the U S Army laboratories. The human hemolytic system is used and the blood sera are inactivated by heating at 56°C for one-half hour. The antigen used is an alcoholic extract of cultures of *Endamoeba histolytica* grown upon the Boeck-Drbohlav medium.

MATERIAL

The greater number of the individuals tested have been patients in Walter Reed U S Army General Hospital where the test is now used as a routine procedure in suspicious cases. The material has included pa-

tients suffering from a great variety of disease conditions and in addition numerous normal persons have been used as controls. The result of each test is checked by microscopic and cultural examinations of the feces of the individuals tested for the presence or absence of *Endamoeba histolytica*, and the results reported in this communication have all been checked by such examinations.

RESULTS OF THE TEST

Considerably more than 1000 individuals have been tested to date, but this report will concern only those tests in which the feces have been checked for the parasite, numbering 786, of which 110, or 13.9 per cent, gave a positive reaction, while 676, or 86 per cent, gave a negative reaction.

In the vast majority of cases the reaction with this test is very clear cut, being either three plus or four plus when read on a four plus scale. Of the 110 positive cases, no less than 91 gave a four plus reaction and 17 a three plus reaction. It should be remembered in considering the number of positive cases that many of the patients at the Walter Reed General Hospital are soldiers or officers who have served in tropical regions, and that in the vast majority of cases tested there were symptoms indicating some disease condition located in the gastro-intestinal tract.

In the 110 positive cases, a check of the feces for *Endamoeba histolytica* resulted in the demonstration of this parasite in 94 cases, or 85.4 per cent. In 16, or a little over 14 per cent, we were unable to find the parasite, although this negative finding cannot

be considered as conclusive owing to the fact that in most of these cases it was not possible to make more than one or two examinations of the feces. It has been definitely shown that a single examination of the feces is often negative in positive cases and that a single examination demonstrates only about one-third of the total infections with this parasite.

Of the 94 positive cases showing the presence of *Endamoeba histolytica* in the feces, 66 showed infection with *Endamoeba histolytica* alone; 12 were mixed infections with *Endamoeba histolytica* and *Endamoeba coli*; 6 with *Endamoeba histolytica* and *Endamoeba nana*; 2 with *Endamoeba histolytica*, *Endamoeba nana* and *Endamoeba coli*, 2 with *Endamoeba histolytica* and *Chilomastix mesnili*; 4 with *Endamoeba histolytica* and *Giardia intestinalis* and 2 with *Endamoeba histolytica* and *Trichomonas hominis*.

There were 676 individuals tested giving a negative result, and of these, *Endamoeba histolytica* was found in 8 cases or 1.1 per cent. Three of these were acute cases of amebic dysentery; one was a case of abscess of the liver; three showed indefinite gastro-intestinal symptoms, while one was symptomless. From these findings it is evident that all persons infected with this parasite do not give a positive reaction but that the percentage of such individuals is apparently very small.

Of the 676 patients giving a negative reaction no less than 220, or 32.5 per cent, were infested with other species of protozoa. There were 100, or 14.7 per cent infested with *Endamoeba coli*; 64, or 9.9 per cent,

infested with *Endamoeba nana*; 3, or 0.4 per cent, infested with *Iodamoeba williamsi*; 26, or 3.8 per cent, with *Chilomastix mesnili*; 16, or 2.3 per cent, with *Trichomonas hominis*, and 11, or 1.6 per cent, with *Giardia intestinalis*. There were 14 mixed infestations with *Endamoeba coli* and *Endamoeba nana*; 6 with *Endamoeba coli* and *Chilomastix mesnili*; 4 with *Endamoeba coli* and *Giardia intestinalis*, and 3 with *Endamoeba coli* and *Trichomonas hominis*.

The infestation of the intestine of man by species of amebae other than *Endamoeba histolytica* does not result in a positive complement fixation reaction. Thus, of the 676 patients giving a negative reaction no less than 164, or 23.5 per cent, were infested with some other species of ameba, but none of these cases gave even a partial reaction with the test.

As practically all of the 676 individuals giving the negative reaction were patients in a large general hospital and were suffering from a wide range of acute and chronic disease conditions, it is justifiable to conclude that this test is not positive in other diseases with the exception, as noted later, of certain rare cases of syphilitic infection.

DISAPPEARANCE OF THE COMPLEMENT FIXATION REACTION AFTER TREATMENT

It has been our invariable experience that after treatment resulting in the disappearance of *Endamoeba histolytica*, the positive complement fixation reaction becomes negative. The rapidity with which the reaction becomes negative depends on the

efficiency of the treatment. The earliest disappearance of the reaction after cessation of treatment resulting in the disappearance of *Endamoeba histolytica* from the stools has been five days and the longest period 60 days. In the longer periods it is probable that the reaction disappeared much more rapidly than indicated, as in some of these cases tests were not made until a long period had elapsed. In most of the cases the reaction disappears within three weeks after the disappearance of the organism from the feces following treatment. In several cases relapses have occurred and the reaction has again become positive, becoming negative again after proper treatment. The disappearance of the positive reaction after treatment demonstrates the specificity of the reaction. It has been noted that in cases giving a positive Wassermann and Kahn reaction that the complement fixation reaction for *Endamoeba histolytica* has become negative while the Wassermann and Kahn reactions remain positive. Table I illustrates the results obtained with the complement fixation test before and after treatment, the cases selected being those most typical of the varying results as regards time of disappearance of the reaction.

RELATION OF THE WASSERMANN AND KAHN REACTIONS

The antigen used in the complement fixation test for infection with *Endamoeba histolytica* is an alcoholic extract of cultures of the organism mixed with the bacteria which may be growing with it in the cultures and it also contains some material derived

from the culture medium itself. Early in our work it was believed that the results obtained with the test might be due to a non-specific substance present in the extract, similar to those in extracts used as antigens for the Wassermann and Kahn tests. In order to obviate such a source of error, and ascertain whether the positive results were due to syphilis, all of the sera tested have been subjected to both the Wassermann and Kahn tests in addition to the complement fixation test for *Endamoeba histolytica*. This check has shown that 15, or 13.6 per cent, of the 110 individuals giving a positive reaction with the complement fixation test for *Endamoeba histolytica* also gave a positive Wassermann and Kahn reaction, while 95, or 86.3 per cent, gave a negative Wassermann and Kahn reaction. On the other hand, of the 676 individuals giving a negative reaction with the complement fixation test for *Endamoeba histolytica*, 56, or 8.2 per cent, gave a positive Wassermann and Kahn reaction, while 620, or 91.7 per cent, gave a negative Wassermann reaction and 618, or 91.4 per cent, gave a negative Kahn reaction. It will thus be seen that about five per cent more individuals gave a positive Wassermann and Kahn reaction in those giving a positive result with the complement fixation test for *Endamoeba histolytica* than in those giving a negative result. It was also significant that of the 15 individuals giving a positive reaction with all three tests, no less than nine failed to show *Endamoeba histolytica* in the feces, although it must be stated that in these cases not more than two

examinations were made of the feces. If we admit that all found negative were free from infection with *Endamoeba histolytica*, it would follow that the positive reactions were due to infection with syphilis, but in interpreting these figures it should be remembered that a considerable number of the sera tested were selected at random from specimens submitted to the Serological Laboratory of the Army Medical School, for the Wassermann and Kahn tests. However, the fact that a considerably larger percentage of cases giving a positive reaction with this test also gave positive Wassermann and Kahn reactions, taken with the failure to find *Endamoeba histolytica* in the feces in more than half of these cases, leads us to conclude that, in rare instances, patients suffering from syphilis may give a positive result with this test and that this disease should be eliminated, if possible, in patients giving a positive reaction, unless the result is supported by finding the parasite in the feces.

PRACTICAL VALUE OF THE COMPLEMENT FIXATION TEST FOR AMEBIASIS

At the present time the practical value of the test we have been discussing is limited by the difficulty of preparing the antigenic extract, which has to be prepared from a large number of cultures of *Endamoeba histolytica*, and the difficulty of maintaining these cultures is not inconsiderable even to one accustomed to cultivating this organism. However, this difficulty is not insuperable, but the technique of the test is such as to

render it impossible of application except in laboratories where the services of a protozoologist and a serologist are available. As shown by the results which have been obtained with the test, it is of considerable value in the diagnosis of cases of amebiasis, and the physicians at Walter Reed General Hospital, for whom the tests have been made, are unanimous in the statement that it has been of practical value to them in diagnosis. Efforts have been made to simplify the method of preparing the antigenic extract, or to render it more powerful, but to date these efforts have been in vain, so that it cannot be said that at the present time the test is on the practical basis that a complement fixation test should be, before it is relied upon alone in the diagnosis of a specific infection. However, it is felt that the technique will be simplified and that eventually the test will be of greater practical value.

CONCLUSIONS

The following conclusions have been justified by the results of the complement fixation test for amebiasis obtained to date

- 1 There occur in the blood serum of individuals infected with *Endamoeba histolytica*, specific substances which can be demonstrated by complement fixation when alcoholic extracts of cultures of this parasite are employed as antigens

- 2 These complement fixing bodies disappear from the blood serum after treatment resulting in the disappearance of *Endamoeba histolytica* from the feces of the infected individuals

3 Individuals free from infection with *Endamoeba histolytica* very rarely give a positive reaction, and in the very small percentage of cases in which infection with this parasite could not be demonstrated it is probable that the failure to demonstrate it was due to an insufficient number of examinations of the feces

4 Individuals infested with *Endamoeba coli*, *Endamoeba nana*, *Iodamoeba williamsi*, *Chilomastix mesnili*, *Trichomonas hominis* or *Giardia intestinalis* do not give a positive reaction with the complement fixation test

5 With the exception of rare cases of syphilis, the complement fixation test for amebiasis does not occur in individuals suffering from other infestations or diseases

6 Positive complement fixation reactions occur in individuals suffering from symptoms of infection with *Endamoeba histolytica*, and also in those in whom symptoms are absent, i e, the so-called "healthy carrier" of the parasite It has been noted that when symptoms are very acute the complement fixation reaction is sometimes absent or weak

REFERENCES

- ¹DOCK, G Centralbl f Bakt, etc, 1891, x, 227
- ²MUSGRAVE, W E Philippine Jr Sci, 1910, v 229
- ³CRAIG, C F Jr Am Med Assoc, 1921, lxxxviii, 19
- ⁴LYNCH, K M Protozoan parasitism

of the alimentary tract, 1930, p 77, New York

- ⁵CRAIG, C F Am Jr Trop Med, 1927, vii, 225
- ⁶CRAIG, C F Am Jr Trop Med, 1929, ix, 277
- ⁷CRAIG, C F Jr Am Med Assoc, 1930, xcv, 10

Pathological Classification of Goiter and Its Clinical Significance*†

By WM CARPENTER MACCARTY, M D , F A.C P., *Rochester, Minnesota*

IN 1912,² a report of more than two thousand goiters revealed that they divided themselves into two great groups: those which were thyroid shaped and those which were nodular. Both groups were then studied from the standpoint of their structural and functional units and these were correlated with the clinical pictures. Since then, 32,479 goiters have been examined grossly and microscopically. In this large amount of material universal facts and principles have been sought in the hope of giving to practicing physicians and surgeons some simple clinical classification based on gross and microscopic characteristics which have become known to be associated with definite symptoms.

It is interesting to note what Boothby,¹ a clinical physiologist, has said about the classification of goiter " . . . the anatomic changes (except infection and malignancy) are not primary and, therefore, are not the fundamental cause of the various diseases of the thyroid gland. In consequence it seems advisable to attempt the interpretation of thyroid disease and the ac-

companying pathologic changes in the light of the changes in physiologic activity rather than in the terms of pathologic anatomy. . . . To meet the needs of the clinician, however, a classification of thyroid disease cannot with the knowledge at present available, be expressed entirely in terms of physiologic activity any better than in terms of gross or microscopic pathology; nor can it be based entirely on etiology."

It is a recognition of this fact over many years that has led to the continued and constant study of gross anatomy, histology and cytology in the series reported. Clinical classifications always become more intelligible when the finer structures, structural relationships, functions, and functional relationships are clearly understood. In this study an attempt has been made to present the fundamentals of structure, and to correlate them with the well-known clinical manifestations of disease of the thyroid gland.

The structural units of the thyroid gland, under all conditions, are very definite and constant. These may be seen in the accompanying diagrammatic drawing (figure 1). Thus in the early stages of fetal development one finds in the neck a mass of cells without acinic or follicular arrangement

*Read before the American College of Physicians, Baltimore, Maryland, March 26, 1931

†From the Section on Surgical Pathology, The Mayo Clinic, Rochester, Minnesota

(figure 1, *a*). These cells are the undifferentiated fetal thyroid gland. Later they assume acinic form (figure 1, *b*). During this change the whole mass of fetal cells assumes the gross form of the adult thyroid gland. During postnatal life this form is maintained unless altered by pathologic conditions. The normal adult thyroid gland is composed of acini which are approximately spheroidal in shape, lined by low cuboidal or spheroidal cells (figure 1, *c*). The lumen of the normal acinus is filled with a "colloid" material. There is fairly constant uniformity of size

of the acini, although one occasionally finds acini which are fetal in size.

In my experience there are only four types or conditions of acini which are sometimes associated with abnormal or pathologic signs and symptoms. These are the fetal acinus (figure 1, *b*) one finds in adenomas, the dilated acinus (figure 1, *d*) found in the simple colloid goiter, the acinus lined by hypertrophic columnar cells (figure 1, *e*) seen in association with hyperthyroidism which occurs in both thyroid shaped goiters and nodular goiters, and the acinus lined by atrophic cells seen in myxedema and cretinism.

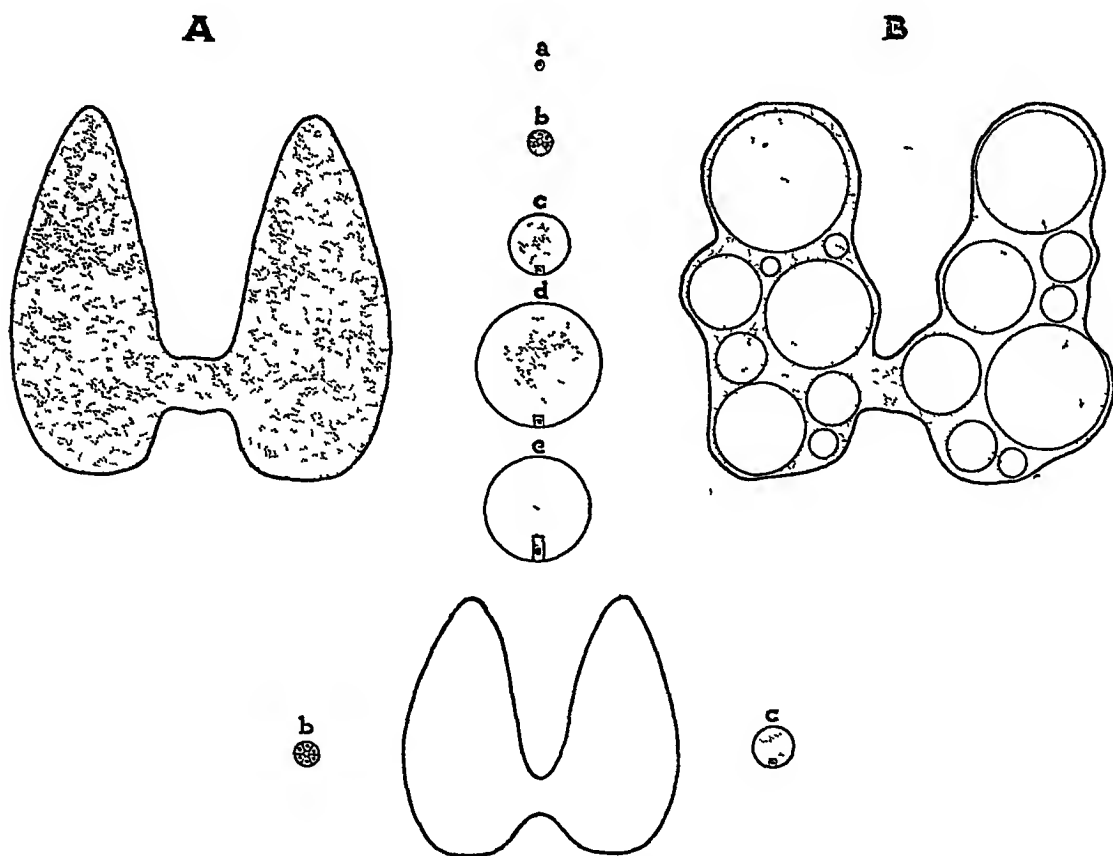


FIG 1 Diagrammatic representation of all types of hypertrophic goiters (with the exception of pure inflammations and malignancies), *A*, hypertrophic symmetric goiters, *B*, hypertrophic nodular goiters, *a*, undifferentiated fetal thyroid cells, *b*, typical fetal acinus, *c*, normal adult acinus, *d*, distended acinus filled with colloid and lined by spheroidal or "cuboidal" epithelium, *e*, acinus lined by hypertrophic or "columnar" epithelium. In the lower portion of the diagram is the relative size of the normal thyroid gland.

ANATOMIC DESCRIPTION

In figure 1, *A* represents thyroid shaped goiter. 1. Hypertrophic* simple or colloid goiter (*Ad*) is one in which there is a symmetric hypertrophy of the whole gland. The acini are dilated or enlarged, lined by low cuboidal cells, and contain colloid. In some of such goiters one also finds fetal and normal acini (*a, b, c*). 2. Hypertrophic parenchymatous goiter (*Ae*) is one in which there is symmetric hypertrophy of the whole gland. The acini are lined by columnar cells and may or may not contain colloid. They may vary greatly in size. All or some of the acini give evidence of parenchymatous hypertrophy. There may be some acini of the fetal (*a, b*), normal (*c*) and dilated type (*d*).

In figure 1, *B* represents nodular goiter. Hypertrophic nodular goiters are due to the presence of spheroidal circumscribed masses which usually can be shelled out. They vary in size; they may be microscopic or many centimeters in diameter. The spheroidal masses (adenomas**) are primarily

*Much confusion arises even in the purest science from lack of definition of terminology. In this paper the term "hypertrophy" whenever used means increase of size, that is, a hypertrophic thyroid gland signifies only that the thyroid gland is enlarged above the normal size. The term applied to cells means the cells are enlarged.

**The term adenoma is usually applied to masses because they are circumscribed and composed of newly formed glandular tissues. Some confusion in the literature has occurred because of disputes over whether this newly formed tissue is circumscribed or not. As a matter of fact it usually is but

composed of fetal acini (*b*) usually separated by loose connective tissue. There may be present others of the different types of acini (*a, c, d*) and in very rare instances acini with hypertrophic cells (*e*). Usually these spheroidal masses show signs of degeneration, which is the result of hemorrhage which destroys the tissues. Such hemorrhagic portions vary in size from petechial points to that in which the whole mass is involved. Such a mass may, therefore, be a cyst containing a hemorrhagic fluid and, in some instances, a brownish clear fluid containing crystals of cholesterol, depending on the length of time since the initial hemorrhage and destruction. In some instances, when the hemorrhage has been small, the region of destruction undergoes repair, and is filled in with scar tissue which sometimes becomes calcified. Small hemorrhagic portions often appear as yellowish spots, this being due to the presence of fatty degeneration of the cells to which the circulation has been impaired. Sometimes the spots are dark blue or purplish-blue, due to an early stage of disintegration of extravasated hemoglobin.

The glandular tissue surrounding the spheroidal masses may present any of the acini seen in the hypertrophic thyroid shaped goiters (figure 1, *A*). An anatomic classification follows

one does find areas in some thyroid glands (particularly pathologic) which are not circumscribed. This is particularly true of the rare thyroiditis. It seems that the discussion is without practical importance and serves merely to confuse working knowledge.

- A (Thyroid shaped) { Hypertrophic colloid goiters
Hypertrophic parenchymatous goiters
Atrophic parenchymatous goiters
- B (Nodular) { Adenomatous goiters without parenchymatous hypertrophy
Adenomatous goiters with parenchymatous hypertrophy { intra-adenomatous
extra-adenomatous
Adenomatous goiters with parenchymatous atrophy { intra-adenomatous
extra-adenomatous
- C Thyroiditis { acute { nontuberculous
chronic { tuberculous
- D Malignancy { carcinoma
sarcoma } usually in degenerating adenomas
epithelioma }
- E Accessory thyroid tissue

The relative frequency of pathologic conditions of the thyroid gland is as follows

ministration of iodine, the parenchymatous hypertrophy usually disappears, although some or all of the symptoms

	Specimens
Hypertrophic colloid goiter (figure 1, <i>Ad</i>)	800 (24 per cent)
Hypertrophic parenchymatous goiter (figure 1, <i>Ae</i>)	9,520 (29.3 per cent)
Hypertrophic nodular goiters (figure 1, <i>B</i>)	21,787 (67 per cent)
Without parenchymatous hypertrophy (figure 1, <i>Be</i>)	18,444 (84.6 per cent)
With parenchymatous hypertrophy (figure 1, <i>Bc</i>)	3,343 (15.4 per cent)
Carcinoma	267 (0.8 per cent)
Sarcoma	7
Epithelioma	7
Tuberculosis	22
Undifferentiated thyroid gland (figure 1, <i>a</i>)	58
Hypertrophic fetal thyroid gland	1
Total number resected thyroid glands (1911-1930 inclusive)	32,479

CLINICAL CORRELATION

Enlargement of the thyroid gland of any type, especially when part of it is substernal, is frequently associated with symptoms and signs of pressure on the respiratory and circulatory apparatus

The clinical syndrome known as hyperthyroidism, and frequently spoken of as a toxic condition, is associated with parenchymatous hypertrophy regardless of whether the goiter is thyroid shaped or nodular. After the ad-

ministration of iodine, the parenchymatous hypertrophy usually disappears, although some or all of the symptoms and signs may remain. Thus, a goiter which previous to the administration of iodine may give evidence of typical parenchymatous hypertrophy presents itself as a hypertrophic colloid goiter after the administration of iodine.

Parenchymatous atrophy is associated with hypothyroidism, which manifests itself in two forms, cretinism and myxedema, and these conditions may occur in thyroid shaped thyroid glands or goiters, or in nodular goiters. In fact, a clinical condition of hypothy-

roidism is sometimes found even in the presence of parenchymatous hypertrophy. Thus, a cretin's thyroid gland may present the histologic picture of typical exophthalmic goiter. There is apparently a quantitative as well as qualitative relationship between parenchymatous hypertrophy and the clinical syndromes of hyperthyroidism and hypothyroidism.

As a result of these generalizations, the clinician may visualize and palpate the neck, determine if possible the

form of the enlarged thyroid gland, decide whether it is thyroid shaped or nodular, and then determine whether the patient has or has not signs and symptoms of hyperthyroidism, hypothyroidism or pressure, and correlate their presence or absence with the diagrams (figure 1). Thus, in a very high percentage of instances, he should be able to forecast the gross and histologic pathologic characteristics. There will be a small error because even a thyroid shaped gland may con-

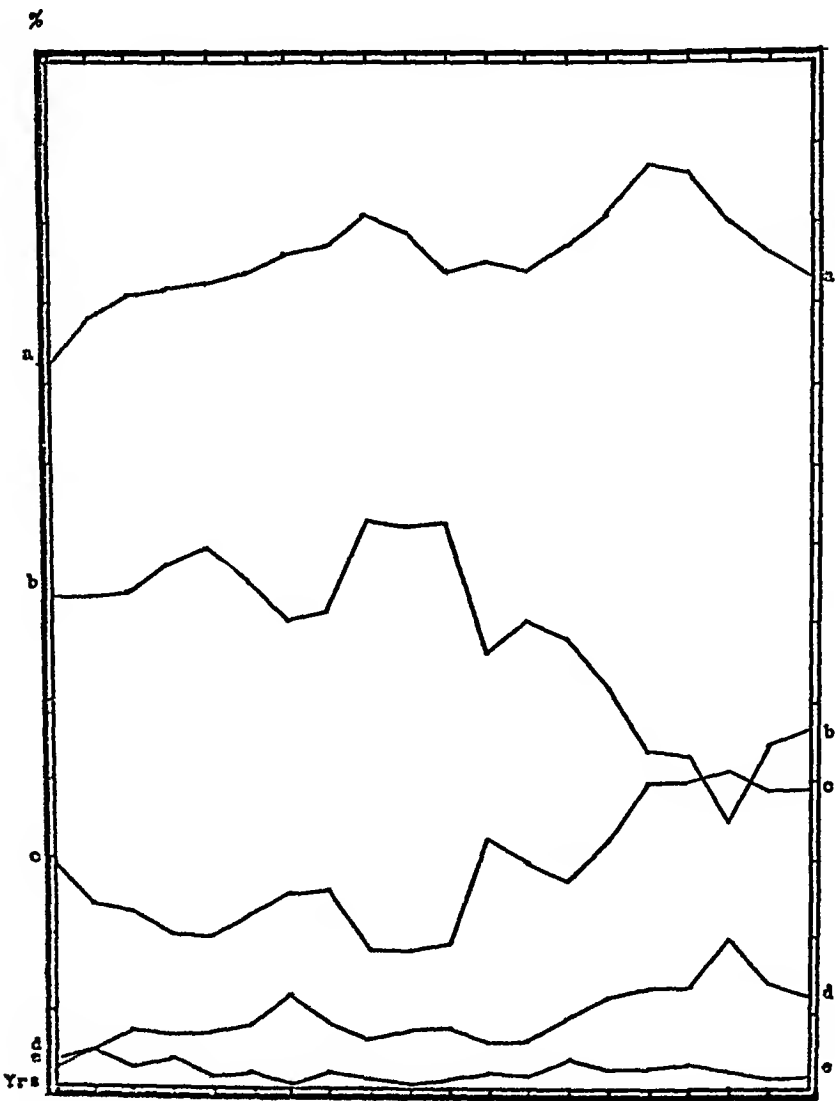


FIG. 2 Relative frequency of parenchymatous hypertrophy in goiters from 1911 to 1930 inclusive, aa, number of resected goiters; bb, percentage of simple nodular goiters without parenchymatous hypertrophy, cc, percentage of simple hypertrophic goiters with parenchymatous hypertrophy; dd, percentage of nodular goiters with parenchymatous hypertrophy; ee, percentage of simple hypertrophic colloid goiters

tain a small impalpable adenoma. There is also the possibility that hyperthyroidism or hypothyroidism may not be sufficiently marked to be recognized clinically. Again, it is possible occasionally to mistake other obscure toxic conditions for hyperthyroidism.

It is of interest, and may be of future importance to note, that during this study over a period of twenty years (1911 to 1930 inclusive), there have been some variations in the relative frequency of the presence of parenchymatous hypertrophy, both in the thyroid shaped goiters and the nodular goiters. Figure 2 shows the percentage of hypertrophic colloid goiters, hypertrophic parenchymatous goiters, and parenchymatous hypertrophy in nodular goiters. Thus, there is an apparent increase in the presence of parenchymatous hypertrophy in both groups of goiters, beginning about 1921. The studies during the whole period of twenty years were made under the guidance of the same staff, and al-

though acuity of vision might have increased with experience it does not seem that the variation should be quite so pronounced. This increase suggests, as H. S. Plummer³ has frequently pointed out, that there might be epidemics of hyperthyroidism. Further regional studies are being made to substantiate or refute this possibility.

It is the object of this short review of a very large amount of material to give the active practicing clinician the fundamental universal facts which have so frequently been confused by elaborate discussions, dissertations, articles, and monographs on the subject of goiter.

BIBLIOGRAPHY

- ¹BOOTHBY, W. M. The thyroid problem. Collected Papers of Mayo Clinic, 1928, xx, 495-515.
- ²MACCARTY, W. C. Goiter and its relation to its structural and physiological units, Surg., Gynec., and Obst., 1913, xvi, 406-411.
- ³PLUMMER, H. S. Personal communication.

The Heart in Hyperthyroidism*†

By HENRY M. THOMAS, Jr., *Baltimore, Md*

IN discussing the heart in hyperthyroidism I shall try to take up clinical points about which there has been much controversy in the past. In order to establish a proper background I shall briefly summarize the history of this subject

In the first allusion to hyperthyroidism made by Parry¹ in 1786 (and published posthumously in 1825) eight cases of a peculiar heart disease, attended by exophthalmos and thyroid enlargement were described. He evidently considered the disease primarily a cardiac affection with secondary exophthalmos and enlargement of the thyroid gland. Although Adleman² in 1829 spoke of "Kropfherz," the Englishmen, Graves,³ Stokes,⁴ Marsh⁵ and McDonnell,⁶ who seem to have written separately between 1840 and 1855 about the same group of cases, still thought the enlargement of the thyroid gland and the exophthalmos came after the heart trouble. In this country Markham,⁷ in 1858, reported "affection of the heart with enlarged thyroid and thymus glands and prominence of the eyes." Moebius⁸ and later Horsley⁹ and Kocher¹⁰ and Müller¹¹ recognized

the part played in the syndrome by the thyroid, but an accurate conception of the heart changes was far from being elaborated at that time. The surgeon, Rose,¹² working at Zurich, wrote a long paper in 1877 pointing out the importance of considering the heart in operations on the thyroid gland. He thought that the goiter compressed the trachea and thus, by interfering with the breathing, placed the right heart under strain. His method of treatment was to perform a preliminary tracheotomy to relieve the heart of this particular form of strain. Thus the so-called goiter heart of Rose was a heart enlarged and weakened purely by a mechanical obstruction. Many other writers noticed decompensation of the heart in patients with large goiters. These observations were practically all made in the goiter regions in Switzerland, the Tyrol, Bavaria, etc., by Wolfier,¹³ Wette,¹⁴ Thomas, Schranz¹⁵ and others. Finally Kraus,¹⁶ in 1899, brought forth his conception of the so-called neurotic or thyrotoxic heart. His view has been generally accepted although there is still some confusion about those cardiac conditions which occur in patients with goiters which are obviously not toxic. I allude to such frank cases as the heart in cretins with goiters, etc. It is likely that the authors from goiter districts

*Read before the Committee on Cardiac Clinics, New York Tuberculosis and Health Association, January 27, 1931.

†From the Thyroid Clinic, Johns Hopkins Hospital.

are describing cases of myxedema heart without clearly differentiating them from hyperthyroid heart. Even as late as 1926, European writers (Meyer and Sulger,¹⁷ and Andrassy) have considered the cardiac disturbances in goiter due to pressure on the trachea, the great vessels, or the vagus and sympathetic nerves of the neck.

In America we have come to a fairly clear differentiation between hyperthyroid heart and myxedema heart and most of us still maintain open minds as to the occasional occurrence of a purely mechanical thyroid heart. Of these three forms of thyroid heart disease, by far the most common is the one associated with hyperthyroidism, and, therefore, I shall limit my discussion to this variety. We do not believe that there is any essential difference between hyperthyroidism from a nodular goiter and that from the diffuse goiter of Graves' disease. The fact that a nodular goiter may exist for a long time before cardiac symptoms develop has led some people to believe that nodular goiter may damage the heart. We have seen no proof of this and are inclined rather to believe that a mild degree of hyperthyroidism which has existed for some years finally becomes evident when the cardiac reserve has been diminished.

If I may state the conclusion at the outset of my discussion, I can then build up the full clinical picture in what I think is its logical sequence. This conclusion is

The primary effect of hyperthyroidism on the circulatory system is tachycardia. This tachycardia is effected in several ways

(a) By additional work associated

with an increase in blood flow caused by the elevated body metabolism;

(b) By stimulation of the accelerator fibers of the sympathetic nervous system;

(c) By direct action of an excess of thyroxin on the heart muscle cells.

I can not substantiate with experimental data the statement that the heart rate goes up in response to an elevated metabolic rate. Some years ago Sturgis¹⁸ pointed out that the increase in heart rate paralleled the elevation in the metabolic rate. But it is perfectly obvious that the same factor which had an effect on the metabolism might quite independently have an effect on the heart rate. In this connection it is interesting to consider the effect of thyroid medication on cases of heart block. Willius,¹⁹ and Aub and Stern²⁰ have reported the results of such treatment and we have had one case in our clinic. Briefly, the ventricular rate is unaffected by large doses of thyroxin although the metabolism goes up and the blood flow increases, the auricular rate, on the other hand, which is still under the control of the vagus and accelerator nerves, increases from 70 to 120. I do not believe that any final conclusions can be drawn from these facts, and I am under the impression that most observers believe that the usual response to the increased blood flow is an increased heart rate. There are various indications of the effect of the accelerator fibers on the tachycardia of hyperthyroidism. Ergotamine has been used to block the accelerator impulses and in some cases a slowing of the heart rate has been accomplished. The over-activity of the sympathetic sys-

tem in other ways has been given as circumstantial evidence of over-activity of the accelerator fibers. But the effect of thyroxin on the heart muscle itself has been clearly demonstrated by Lewis and McEachern²¹ Experiments with isolated hearts from animals which have been rendered hyperthyroid by feeding with thyroid extract show that these heart muscle preparations maintain a rapid rate of contraction (26 to 144 beats per minute faster than normal preparations under the same conditions) for as long as ten hours, the longest period over which they have been observed as yet. This suggests an increase in the heart muscle cell metabolism

Now, as the hyperthyroid tachycardia persists, however it may have been produced, the rest of the signs and symptoms of thyroid heart gradually come into the picture. If the patient is a young, healthy individual, his heart will be able to stand even an excessive degree of hyperthyroidism without evidence of congestive heart failure. If he is past middle age and his heart therefore is out of training and unused to the excessive strain which the constant running around of young individuals produces; or, on the other hand, his heart is the site of valvular or arteriosclerotic heart disease with diminished cardiac reserve, then, sooner or later, congestive heart failure will occur. In practically every instance this is associated with, or preceded by, auricular fibrillation. It is not clearly known whether auricular fibrillation is purely a failure of the auricles to respond to too much work or whether thyroxin adds a degree of irritability to the muscle fibers which

causes them to fibrillate sooner than otherwise. The fact that young, healthy hearts rarely fibrillate even under the most severe degree of hyperthyroidism lends weight to the idea that it is purely an over-work phenomenon which occurs only when the cardiac reserve has been overdrawn. Seven and a half percent of the cases of auricular fibrillation recorded in the Heart Station of the Johns Hopkins Hospital were patients suffering from hyperthyroidism (McEachern).

Among the cases which develop auricular fibrillation some do not show signs of congestive heart failure. Hamilton²² has stressed this point and carefully described the clinical picture of those with congestive failure. He points out that in his series of 50 such cases, exophthalmos was usually absent, the thyroid gland was often normal in size, the tremor and nervousness almost never occurred. In recognizing this condition from the other causes of congestive heart failure, he stresses (a) tachycardia which does not respond as well as would be expected to complete rest and digitalization, (b) history of unexplained loss of about 30 pounds, (c) history of a surprisingly long duration of complete disability associated with gross signs of heart failure, (d) elevated BMR (he states that non-thyrotoxic congestive heart-failure cases may have a BMR of +64 which will return to normal when the heart failure is relieved). The average age of this series of Hamilton's cases was 50 years. One might suppose that this group (like many cases of so-called toxic adenoma) is comprised of patients whose cardiovascular systems were damaged to a

degree whereby slight hyperthyroidism (so slight that the characteristic clinical signs of exophthalmos, goiter, tremor and restlessness are hardly noticeable) could cause myocardial insufficiency. This series of Hamilton's brings out the fact more clearly that when congestive heart failure occurs in hyperthyroidism, the failure is brought about, not by excessive hyperthyroidism, but by moderate or slight hyperthyroidism superimposed on an inferior cardiovascular system

Whether or not dilatation and hypertrophy occur in uncomplicated thyroid heart is still an unsettled question. Those who think that hypertrophy of the ventricles occurs can find confirmation in the experiments on laboratory animals. Cameron and Carmichael²³ in 1921 produced hypertrophy of the heart in rats by feeding thyroid extract. Last year Simonds and Brandes²⁴ reported their work on dogs. They found that the hypertrophy involved all the chambers of the heart with a slightly greater proportional increase in the left ventricle. Also most accounts of the postmortem findings of the thyroid heart describe hypertrophy in a large number of the cases and of 27 thyroid hearts studied in the Pathological Department of the Johns Hopkins Hospital by McEachern and Rake,²⁵ 16 had definite hypertrophy. Lewis²⁶ reported 12 cases, in all but three of which the heart weighed over 300 grams. Means and Richardson²⁷ also have reported the necropsy findings in 12 cases. Their series showed but little hypertrophy. The clinical evidence is not clear cut. Hurxthal²⁸ made careful cardiac measurements on thyroid patients before

and three months after operation. He found no contraction in the size of the heart, from which he inferred that there had been no previous enlargement. He further compared 100 cases of toxic goiter with 100 cases of non-toxic goiter and, after making correction for the transverse diameter of the chest and body weight, he concluded that the average transverse diameter of the heart in the toxic group exceeded that of the non-toxic group by only 0.49 cm. It seems likely to us that the hypertrophy has occurred only as a result of a well marked and fairly profound hyperthyroidism. We can say definitely that when congestive heart failure occurs dilatation of the ventricles is very likely to be found and this dilatation disappears entirely when the hyperthyroidism has been removed.

The blood pressure shows a slight elevation in the systolic pressure and diminution in the diastolic pressure. If a pronounced degree of hypertension is encountered it is likely that this condition will persist or become worse after operation. The electrocardiogram shows an unusually prominent T wave and Hamberger²⁹ has noted a parallel in the degrees in basal metabolic rate and the height of the T wave following iodine medication and thyroidectomy.

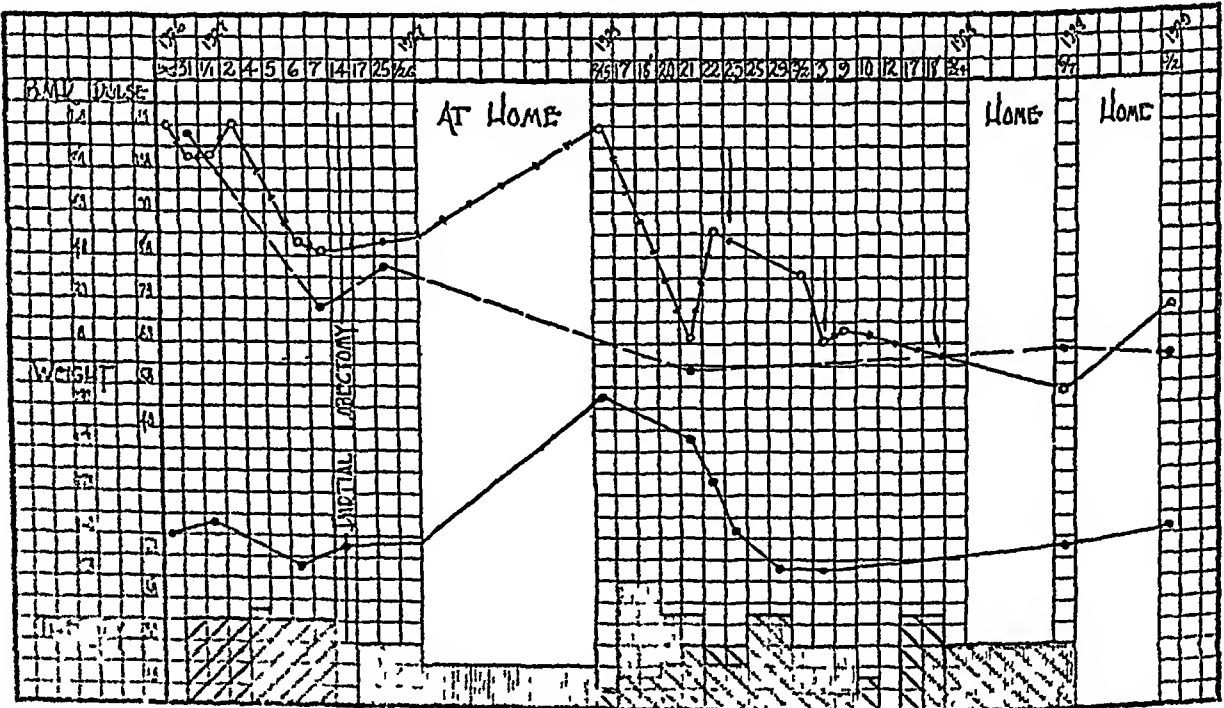
If the hyperthyroidism is successfully terminated by subtotal thyroidectomy and adequate post-operative treatment is observed, the heart will, sooner or later, return to the state in which it was found at the beginning of the hyperthyroidism, allowing only for changes which would have occurred in a similar length of time under other

conditions This statement is a brave one. Let me show a condensed chart of such a patient.³⁰ (See chart 1).

Careful search for pathological changes in the hearts of patients dying from hyperthyroidism has yielded very inadequate findings. Various reports have been made noting changes in the heart muscle and these reach their high point with Goodpasture's³¹ account of two cases which showed degeneration and necrosis of the heart muscle fibers. Current opinion is that patients dying from thyrotoxic heart failure show a variety of inconstant minor lesions, none of which can sure-

ly be ascribed to hyperthyroidism. Some of the changes described are cardiac dilatation and hypertrophy, slight round cell infiltration and hyaline and fatty degeneration of the muscle fibers. An exhaustive examination of all the hearts of patients dying with hyperthyroidism at the Johns Hopkins Hospital has recently been made by McEachern and Rake²⁵. This work is soon to be published in a monograph form. Stated briefly their conclusions are that no pronounced pathological change is produced in the heart by hyperthyroidism.

If you will accept the foregoing



--- Pulse Rate, --- Body Temperature, --- Weight, [diagonal lines] Lugol's, [horizontal lines] Te. Digitalis, [cross-hatch] Quinidine Sulfate

CHART I

Following the partial lobectomy the patient insisted on returning home before the auricular fibrillation had been interrupted. During the 13 months at home on digitalis, under the direction of his local physician, he continued to fibrillate and gradually went down hill. During his second stay at the hospital on rest, digitalis and quinidine, he excreted 33 pounds of fluid in 8 days and reverted to normal rhythm on the 8th day. Since September 12, 1929, he has done full manual labor as a track man on the railroad without the loss of a single day from sickness and without taking either digitalis or quinidine. (This chart was drawn by Mr. Charles McCurdy Gray, a member of the post-graduate class of the Johns Hopkins Medical School. Reprint from Bulletin of the Johns Hopkins Hospital, 1930, xlviii, 1-16)

hypothesis of the heart in hyperthyroidism the road to proper treatment will be quite clear. The first principle is that until congestive failure occurs no specific treatment for the heart is indicated; the second principle is that when once congestive heart failure has occurred it should be treated like any other form of congestive heart failure. I should like to make one exception to this statement and warn against the pre-operative use of quinidine for auricular fibrillation. The reason for this is that in the face of hyperthyroidism a fibrillating heart can be better controlled by digitalis than a heart with a regular mechanism. For example the ventricular rate of a case of auricular fibrillation in hyperthyroidism can be slowed under digitalis to 70 or 80 or 90 beats to the minute and the circulation greatly improved in this way. If, then, this digitalized heart is made to revert to normal mechanism by quinidine the slowing effect of digitalis may be lost and the rate suddenly jump up to 160 or 180. I have seen one such case in which just such a change took place, followed in the course of a few hours by exitus. When suitable therapeutic measures have been applied for relief of the heart failure the more important treatment of the hyperthyroidism can be undertaken. One must not be too cautious as to surgical procedures in cases of this kind as they are surprisingly well borne by these patients and they alone offer permanent relief.

Friedrich Muller and others have made the statement that iodine occasionally has a deleterious effect on the heart muscle. Laboratory animals have

been given relatively enormous doses of iodine with the production of slight pathological changes in the heart muscle, noticeable by microscopic examination. In the Johns Hopkins Cardiographic Laboratory a number of observations have been made on normal individuals before and after taking large doses of Lugol's solution^{32,33}. No changes were found in the electrocardiographic tracings or in other heart examinations in this series despite the fact that several of the individuals proved to be hypersensitive to iodine and suffered from varying degrees of skin eruptions and gastro-intestinal upsets. Dr John T. King, Jr.,³⁴ observed a case of an elderly woman suffering from nodular goiter with hyperthyroidism. After four days of rest in bed and Lugol's solution, ten minims three times a day, her heart rate became absolutely irregular. The Lugol's solution was discontinued and, in three days, the heart returned to normal rhythm. Of course this one case is not conclusive, but it illustrates very well my feeling in this matter. I believe that to a thyrotoxic heart iodine may be the additional factor which causes the final break. It seems quite likely to me that most of the cases of so-called iodine hyperthyroidism (Jod-Basedow) are in reality iodinism superimposed on hyperthyroidism.

We finally may conclude that the heart, like the rest of the body, responds to hyperthyroidism by being speeded up. Given a normal young cardiovascular system, this speeding up is a matter of little or no consequence. On the other hand, given a heart which is weakened by advancing age or heart disease and then the constant accelera-

tion from hyperthyroidism frequently leads to congestive heart failure. In either instance removal of the hyperthyroidism allows the heart to regain, both functionally and structurally, its pre-hyperthyroid condition.

I wish to express my indebtedness for criticism and suggestions during the preparation of this paper, to Dr Donald McEachern of the Johns Hopkins Hospital Medical House Staff, whose original work and whose familiarity with the literature on this subject made his help of great value

BIBLIOGRAPHY

- ¹PARRY, C H Collections from the unpublished writings of the late C H Parry, Underwood, London, 1825
- ²ADLEMANN, G. Beitrage zur Pathologie des Herzens, der Schilddruse und des Gehirns, Jahrbucher der Philosophisch-Medizinischen Gesellschaft zu Wurzburg, 1928, 1, 104-108
- ³GRAVES, R J Clinical Lectures, Lond Med and Surg Jr. (Renshaw's), 1835, vii, 516 Also. Clinical Lectures delivered during the Sessions of 1834-5 and 1836-7, Philadelphia, 1838
- ⁴STOKES, W Diseases of the heart and the aorta Dublin, 1854, p 278
- ⁵MARSH, SIR HENRY Dilatation of the cavities of the heart—Enlargement of the thyroid gland, The Dublin Jr of Med Sci, 1841, xx, 471
- ⁶MCDONNELL, J. D Observations on a peculiar form of disease of the heart, attended with enlargement of the thyroid gland and eyeball, Dublin Jr of Med Sci, 1845, xxxvii, 200
- ⁷MARKHAM, W O Affection of the heart, with enlargement of thyroid and thymus gland, and prominence of the eyes, Trans Path Soc, London, 1857, ix, 163
- ⁸MORBIUS, P. J. Über insuffizienz der Konvergenz bei Morbus Basedowii, Centralbl f Nervenl, 1886, ix, 356 Also Die Basedow'sche Krankheit, Vienna, Ed 2 H Holder, 1906
- ⁹HORSLEY, SIR V. The thyroid gland, its relation to the pathology of myxedema and cretinism, to the question of the surgical treatment of goitre, and the general nutrition of the body, Brit Med. Jr. 1885, 1, 111
- ¹⁰KRELL, T Über Kropfextirpation und ihre Folgen, Arch f. Klin. Chir. 1883, 257, 251
- ¹¹MULLER, F Beitrage zur Kenntniss der Basedow'schen Krankheit, Deutsch Arch f klin Med, 1893, li, 335
- ¹²ROSE, E Über den Kropftod und die Radicalcur der Kropfe, Arch f. klin Chir, 1878, xxii, 1
- ¹³WOLFLER, A Zur chirurgischen Anatomie und Pathologie des Kropfes und Nebenkropfes, Arch f klin Chirurgie, 1890, xl, 346-428
- ¹⁴WITTE, THEODORE I Beitrage zur Symptomatologie und chirurgischen Behandlung des Kropfes, Arch f klin. Chirurgie, 1892, xlii, 652-716
- ¹⁵SCHRANZ, JULIUS Beiträge zur Theorie des Kropfes, Arch f klin Chirurgie, 1886-87, xxxiv, 92-159
- ¹⁶KRAUS, F Über Kropfherz, Beziehungen zwischen Struma und Morb Basedowii, Wien klin Wchnschr., 1899, xii, 416
- ¹⁷MEYER, A W, and SULGER, E. Goiter heart before and after operation, Med. Klin, 1926, xxii, 838-840 (Abst) Jr Am Med Assoc, 1926, lxxxvii, 372
- ¹⁸STURGIS, C C, and TOMPKINS, E H A study of the correlation of the basal metabolism and pulse rate with hyperthyroidism, Arch Int Med, 1920, xxvi, 467
- ¹⁹WILLIUS, F A. Heart in thyroid disease, Ann Clin Med, 1923, i, 269
- ²⁰AUB, J C, and STERN, N. S The influence of large doses of thyroid extract on the total metabolism and heart in a case of heart block, Arch Int Med, 1918, xxi, 130.
- ²¹LEWIS, J. K, and MCEACHERN, D Persistence of accelerated rate in isolated hearts and auricles from thyrotoxic rabbits, response to iodides, thyroxin and epinephrin Johns Hopkins Hospital Bull, in press.

- ²²HAMILTON, B E . Heart failure of congestive type caused by hyperthyroidism, Jr Am Med Assoc , 1924, lxxxiii, 405-410
- ²³CAMERON, A T, and CARMICHAEL, J Comparative effects of parathyroid and thyroid feeding on growth and organ hypertrophy in white rats, Am Jr Physiol , 1921, lviii, 1
- ²⁴SIMONDS, J P, and BRANDES, W W Size of heart in experimental hyperthyroidism, Arch Int Med , 1930, xlv, 503-512
- ²⁵MCEACHERN, D and RAKE, G A study of the morbid anatomy of hearts from patients dying with hyperthyroidism Johns Hopkins Hosp Bull , 1931, xlvii, 273
- ²⁶LEWIS, WILLIAM Hyperthyroidism and associated pathology, Am Jr Med Sci, 1931, clxxxi, 65
- ²⁷MEANS, JAMES H, and RICHARDSON, EDWARD Diseases of the thyroid Oxford Monographs on Diagnosis and Treatment, 1929, Oxford University Press, New York
- ²⁸HURXTHAL, LEWIS N The cardiovascular system in goiter, Tr Am Assoc for the Study of Goiter, 1930, Portland, Ore
- ²⁹HAMBERGER, W W , LEVY, M W , PRIEST, W S, and HOWARD, HELEN C The heart in thyroid disease, Arch Int Med , 1929, xliii, 35-49
- ³⁰THOMAS, HENRY M, Jr Thyroid heart, a transitory condition, Johns Hopkins Hosp Bull , 1930, xlvii, 1-10
- ³¹GOODPASTURE, E W Myocardial necrosis in hyperthyroidism, Jr Am Med Assoc , 1921, lxxvi, 1545-1551 Also Myocardial necrosis, Jr Exp Med , 1921, xxxiv, 407
- ³²MCEACHERN, D The effect of the ingestion of potassium iodide on the pulse rate of normal individuals, Johns Hopkins Hosp Bull , 1930, xlvii, 299-303
- ³³MCEACHERN, D, and BAKER, B M The effect of the ingestion of potassium iodide on the electrocardiogram of normal individuals, Johns Hopkins Hosp Bull , 1930, xlvii, 304
- ³⁴KING, JOHN T, Jr Personal communication.

Medical Aspects of Peptic Ulcer*

By ALBERT F. R. ANDRESEN, M.D., F.A.C.P., *Brooklyn, New York*

IT is almost necessary to make an excuse for writing about peptic ulcer. Medical literature of the past twenty years has been filled with articles on this subject, volumes have been written about it and a verbal war between the advocates of medical and surgical treatment is still being waged with great intensity. When so much verbiage is wasted on any subject it engenders the suspicion that the reason for this wastage is a lack of knowledge or understanding of the subject. In the case of ulcer this is undoubtedly true. So much good research work has been done in regard to the pathology and etiology of ulcer and so well have the findings agreed with clinical experience, that it is surprising to hear even prominent surgeons and clinicians say that the cause is unknown. It is also peculiar that with the multiplicity of articles dealing with the well-known fact that in peptic ulcer there are almost invariably evidences of other inflammatory changes in stomach, duodenum, biliary tract, liver, pancreas, small and large intestine and appendix, it is taking both clinicians and surgeons so long to realize that in considering peptic ulcer as an entity and treating it as such they are not only illogical, but are definitely to blame for the poor results so generally reported.

PATHOLOGY

The pathology of peptic ulcer has not been given the attention it deserves. Lewis Gregory Cole has made a very valuable contribution to our knowledge in his studies of freshly excised ulcers, and parts of stomachs with ulcers, during the past five or six years, and his findings should be more generally made known. Cole divides ulcers into three groups, those of the body of the stomach, "corporic ulcers," those of the prepyloric region, "prepyloric or pyloric ulcers," and those of the first portion of the duodenum, "postpyloric ulcers" or "ulcers of the cap." He has shown that the ulcers are not the result of an erosion of the mucosa, but that they begin as areas of focal necrosis in the stomach or duodenal wall, and that they burst through in the line of least resistance, just as carbuncles or boils break through the skin. The intact mucosa can be seen curled under the edge of the ulcer. The size and depth of the ulcer depend on the site of the original area of focal necrosis and the degree of elasticity of the wall at this point. Thus an area of focal necrosis just under the mucosa breaks through rapidly and produces the small, rapidly healing submucosal ulcer, practically no more than a "canker sore," usually found in the prepyloric region, where there is little opportunity for its spread due

* Accepted for publication February 19, 1933.

to a relatively inelastic wall. An area of necrosis in the deeper layers, especially if in the loose areolar area along the lesser curvature of the stomach, will produce a deeper, wider ulcer. If the area is under the serosa, perforation is liable to result. All ulcers have a remarkable tendency to heal, as shown microscopically by evidences of a reparative process at the base of the ulcers, and as Cole has demonstrated in the living stomach by repeated serial roentgenograms, at short intervals, showing prepyloric ulcers disappearing in from a few days to two weeks and large lesser curvature ulcers in from a few weeks to two or three months. The healing of duodenal ulcers, because of the frequently persistent deformity resulting, is not as clearly demonstrable by radiography, but can be shown by reduced irritability of the duodenum on fluoroscopy and by disappearance from the duodenal contents of the ulcer base slough and blood. By demonstrating in removed stomachs the presence of multiple microscopic ulcer scars, often dozens in one stomach, Cole has arrived at the inevitable conclusion that each recurrent attack of ulcer symptoms is due to a new ulcer and that symptoms persisting or perhaps varying in intensity, are due to new ulcers developing before the older, partially healed ones have ceased to cause symptoms. Contrary to previously conceived notions, the finding of two or more ulcers in various stages of healing, is not at all unusual.

The *complications* of ulcers are easy to understand. *Perforation* has already been mentioned, and has for many years been considered not a

breaking through of an old ulcer, but a separate disease, the occurrence of such a severe ulcer that it immediately punched a hole through the whole stomach wall. Cole's explanation of this type of ulcer as due to an area of focal necrosis just under the serosa and breaking through in both directions, is simple and clear. If the point of perforation is opposite some organ, like liver or pancreas, or if it occurs into the lesser peritoneal sac, only a localized well-walled-off abscess area may result, but frequently the break occurs into the general peritoneal cavity, with resulting general peritonitis.

In the case of large or deep ulcers, especially where these are located at a narrow point, like pylorus or duodenum, although occasionally also in mid-lesser curvature, healing or external inflammatory reaction or both may result in so much cicatricial contraction as to cause obstruction to the onward passage of food—*pyloric stenosis* or *hour-glass constriction*. Acute inflammatory changes at such an area of narrowing or in a large ulcer may at times cause temporary complete stenosis, which may become partial or may disappear as the edema subsides.

Gross hemorrhage from ulcer is comparatively rare, and is due to the fact that the area of necrosis producing the ulcer happened to involve one of the larger vessels of the stomach wall. Hemorrhage will recur until the damage is repaired—usually by the organization of a thrombus in the injured vessel. If the eroded vessel is one running at right angles to the base of the ulcer (a terminal vessel) prompt retraction and cessation of hemorrhage occur, if lying longitudinally, with ero-

sion of its side wall, the hemorrhage will be persistent and often fatal. The vessels of some individuals seem less resistant to infection and these individuals tend to have hemorrhages with each recurrent ulcer. Superficial bleeding and serous exudation occur during part of the cycle of all ulcers.

The possibility of *carcinomatous degeneration* of gastric ulcers has in the past few years been relegated to its proper status. Studies conducted all over the world, and based on both clinical observation and pathological findings, have shown that carcinoma is no more apt to occur in the stomach of an ulcer patient than in the normal stomach, carcinoma having been shown to occur at the most in but four per cent of such cases. Cole, ten years ago, showed by statistics of cases seen by him that gastric carcinoma occurred more frequently in patients who had had operations for ulcer than in those treated medically. If we are to accept Cole's findings, which indicate spontaneous, rapid and complete healing of ulcers, it would give but little time for the development of malignant changes in any given active ulcer, leaving only the scar to act as a nidus

ETIOLOGY

The etiology of ulcer has been another moot point. The older theories considering trauma or irritation as etiologic factors were suddenly confronted, more than sixteen years ago, by Rosenow's demonstration of the etiologic relationship between focal infection and ulcer. Although Rosenow's laboratory experiments have not been universally confirmed by other observers, probably due to their using a

different technique, the clinical experience of those who have, like myself, made the removal of all possible focal infections the *sine qua non* in treatment, has been such as amply to substantiate the claims of such a relationship. Previous to Rosenow's experiments, Fenton B. Turck, showing that areas of focal necrosis could be produced in animals by intravenous injection of solutions of dead tissue (which contain minute amounts of the destructive shock toxin he has named cytolsin), in some instances produced typical indurated gastric ulcers in a few minutes. He concluded that this cytolsin was the causative factor. It seems only reasonable to assume that what may occur at the site of a focal infection, is an absorption of the cytolsin produced in the dead tissue resulting from the infection, and that the secondary focal necroses may be due more to electrochemical reactions of the tissues to this cytolsin than to actual initial migration of bacteria to the intact stomach wall. On the other hand, what relation anaphylaxis due to bacterial or tissue sensitization bears to the problem, has not as yet been satisfactorily determined. However, the results obtained in preventing recurrent ulcer when all possible infective foci have been removed, and the repeated recurrences in spite of any medical or surgical treatment where these foci have been neglected, affords clinical proof of the etiologic relationship between the foci and the ulcers.

PATHOLOGICAL PHYSIOLOGY

The *disturbed function* caused by the presence of an ulcer in stomach or duodenum is due primarily to irrita-

tion, and the results will vary with the degree of irritability of the patient's stomach, his general nervous irritability and the severity of the usually concomitant lesions in other parts of the gastrointestinal tract and its appendages. The most common result of irritation on the *motor function* of the stomach is an increase in the frequency and severity of the normal hunger contractions of the empty stomach, and at times the occurrence of such contractions before the stomach is entirely empty. Also, especially when an ulcer is near the pylorus or beyond it, there is frequently intermittent pylorospasm. In duodenal ulcer, and more particularly in lesions further down in the gastrointestinal tract, retroperistaltic waves (the retrostalsis described by Alvarez) may produce troublesome symptoms.

The effect of ulcer on the *secretory function* of the stomach is to cause an increased irritability of the gastric glands, with a resulting continued secretion, often reaching high levels of acidity, although at times there may be diminution or even an absence of hydrochloric acid in the gastric contents, due either to the exhausting effect of prolonged irritation or to chronic inflammatory changes, involving the gastric glands.

SYMPTOMATOLOGY

The *symptoms* of peptic ulcer are in most cases very characteristic. Epigastric pain, occurring after a longer or shorter interval after eating (usually from one-half to four hours after meals) and promptly relieved by the intake of any food or drink—the “hunger pain” of Moynihan—is practically

pathognomonic of ulcer. This pain is due to exaggeration of the normal hunger contractions of the empty stomach, and its severity and the time of its occurrence are, as mentioned above, dependent upon the irritability of the stomach and also upon the size and frequency of the meals taken, so that while some patients may get a severe pain within an hour after eating, others may feel no pain at all. The location of the ulcer has no effect upon the time pain will occur—gastric ulcers may cause pain three or four hours after meals, duodenal ulcers one or two hours after. If ulcers occurred alone, that is, if there were not, as there invariably is, an accompanying inflammatory reaction in other parts of the gastrointestinal tract, the symptoms would probably always be typical. These other conditions, the inflammations of the biliary tract, pancreas, appendix and colon, not only produce symptoms directly referable to themselves, but cause retrostaltic waves, producing pylorospasm and mild or severe reverse peristalsis in the stomach, resulting in epigastric distress or fulness immediately after meals, aerophagia, heartburn, sour eructations or actual regurgitation or vomiting. Some of them also cause more or less severe bowel symptoms. These other symptoms may be so prominent as to mask or modify the characteristic ulcer symptoms, thus making diagnosis by history alone very difficult. Loss of weight and strength, anemia, and various nervous manifestations are due to the individual patient's reaction to the symptoms—some starve themselves and grow thin and anemic, others overeat and gain weight rapidly. Some con-

sider that as long as food relieves them there is no cause for worry, others suspect cancer and become neurasthenics

The *symptoms of the complications* of ulcer are rather characteristic. In *gross hemorrhage*, hematemesis and melena, usually preceded by severe pain and fainting or collapse, are typical, although in the absence of hematemesis, the characteristic sticky, tarry stools, passed during the night may not be noticed, and the patient may describe only a diarrheal attack with vertigo or syncope.

Perforation, ushered in by a terrific pain, not relieved by the food or alkali which the patient usually tries before the doctor arrives, and which is sooner or later followed by shock and the symptoms of peritoneal irritation, is a condition requiring immediate recognition so that prompt resort may be had to a life-saving operation.

Pyloric stenosis and *hour-glass constriction* present the characteristic symptoms of delayed vomiting, that is, vomiting occurring at an interval after meals when all foods should normally have been expelled from the stomach. Patients with this complication who may previously have vomited soon after eating or at the time of occurrence of the ulcer pain, begin to vomit less frequently, often in the evening, and in the vomitus may be recognized food eaten two or three meals previously or even from the day before. Frequently there is a diminution of the ulcer pains, but a feeling of fulness in the upper abdomen and a more or less marked anorexia.

The occurrence of *carcinomatous change* in an ulcer is accompanied by

an unusual loss of weight and strength, and an increasing pallor, associated either with symptoms similar to those previously complained of or a new train of rather indefinite dyspeptic symptoms, with anorexia. Often gross hemorrhage may be the first symptom of a carcinoma.

DIAGNOSIS

The diagnosis of peptic ulcer is usually made by means of three characteristic findings—the history, examination of gastric and duodenal contents by the fractional method and the roentgen ray examination.

1. The *history* is often of the greatest help in diagnosis. Recurrent attacks of typical hunger pain, that is, pain occurring after an interval of from one-half to three or four hours after meals and relieved by the intake of food, drink or alkali, was long ago described by Moynihan as pathognomonic of ulcer, and in my experience it is extremely uncommon not to be able to demonstrate an ulcer when this symptom is present. The pain is most commonly located in the epigastrium, but at times may be located in the gall-bladder or appendix regions, in either inguinal region, the precordium or the back. Retrostaltic symptoms, as described above, are not characteristic of ulcer, but are more frequently due to the other co-existent gastrointestinal lesions. Vomiting, occurring immediately after meals or at the time of the pain, is one of these retrostaltic symptoms, but if it is of the “delayed” type, is characteristic of stenosis. The symptoms of other complications have been mentioned. A first attack of ulcer symptoms, especially in a patient

of carcinoma age and if continuing over a period of a few months, may be due to a carcinomatous ulcer

2 *Careful fractional gastric analysis*, preceded by examination of the fasting residue after a duration meal of rice and raisins, is of great help in diagnosis. Three findings are studied namely, those relating to motility, to secretion and to admixtures

A *Motility* an overnight residue of gross rice and raisins indicates pyloric stenosis, the degree of which may be determined by the rapidity with which the stomach can expel the test meal subsequently given. In the absence of an overnight residue, delayed expulsion of the test meal indicates marked pylorospasm and the probable presence of a lesion near the pylorus, but not obstructing it

B *Secretion* is indicated by the curve of acidity following ingestion of a test meal or the intramuscular injection of histamine dihydrochloride. In gastric ulcer this curve is not of value there may be a normal curve, there may be no secretion of acid at all or there may be a continued secretion. In pyloric and post-pyloric ulcers we find that a continued secretion, i.e., secretion continuing beyond the normal period of secretory reaction to a stimulus, and often reaching great heights of acidity, is the rule, although here, also, achylia is found at times, especially in long-continued cases

C *Admixtures* The presence in the gastric contents of small, more or less dried particles of blood, with adherent detritus coming from the base of an ulcer, is a valuable finding, but

is difficult to differentiate from blood due to trauma in swallowing the tube. It is, however, of some value in confirming an x-ray finding of gastric ulcer. Where no blood is found in the gastric contents until the normal reflux of bile stained duodenal contents during the second hour after the test meal, and the particles just described are then encountered, we have a very characteristic finding of duodenal ulcer. Gastric analysis is of little or no value in differentiating between gastric ulcer and even well-advanced carcinoma, although the continuous presence of blood is suspicious of malignancy. In rare instances pieces of carcinoma tissue may be aspirated and recognized microscopically. In carcinoma associated with pyloric stenosis, a fasting residue containing no free hydrochloric acid and in which Boas-Oppler bacilli and lactic acid are present, is found in a large proportion of cases

3 *The roentgen ray diagnosis of ulcer* is of great importance. The characteristic findings on a radiographic film are the presence of a *defect*, which represents the displacement of the ingested barium mixture by the area of induration about an ulcer, and a *protrusion* (niche) which represents the crater of the ulcer. In the case of the large (corporic) ulcers which nearly always occur at some point along the lesser curvature, the protrusion may be large (up to 5 cm in diameter) and the defect extensive. In the case of small prepyloric ulcers the protrusion may be very small, the defect barely noticeable. In the duodenal cap the crater is not as frequently seen, but the induration causes persistent deformities which are characteristic

Fluoroscopic examination is subject to grave error in that more than fifty per cent of even large corporic ulcers are not recognized and the small prepyloric ulcers are rarely seen, although the deformity and irritability of the duodenum make ulcers of the cap easily recognizable by this method.

A persistent deep incisure on the greater curvature often indicates the presence of a posterior wall ulcer. In pyloric stenosis due to ulcer a large atonic stomach with a smooth outline at the point of obstruction is the rule, the ulcer crater being less frequently seen than in hour-glass constriction. Where perforation is suspected the barium meal is contraindicated, but a "flat plate" of the abdomen (a safe procedure) will often show an accumulation of gas above the dome of the liver. After a gross hemorrhage, roentgen examination should be deferred for at least two weeks after cessation of the hemorrhage.

Where the defect or crater shows an irregular outline or where there is not a definite decrease in size of a gastric defect in a period of a few weeks, carcinomatous ulcer must be suspected and exploration resorted to in order to clinch the diagnosis.

TREATMENT

The treatment of peptic ulcer resolves itself into three distinct procedures: the local treatment of the ulcer by mechanical means, the removal of the cause and the care of the complications.

1. *The local treatment*, as in the case of an ulcer in any part of the body, consists in putting the ulcer area at rest and in keeping it soothed so as to permit of healing. The stomach is

never entirely at rest, but it is most active, even to the state of tetanic contractions, when empty. The normal hunger contractions are exaggerated in the presence of an ulcer and can best be relieved and prevented by keeping the stomach full of soothing food. The food should be sufficiently nutritious to permit of the body carrying on the healing process effectively, and where the patient is undernourished, should add to his weight. It should, like any diet, contain the proper balance of essential ingredients, and have an adequate vitamin content. While we do not feel that acidity plays any particular part in the production or persistence of an ulcer, combination with free acid and avoidance of over-stimulation of gastric juice are desirable. Daily bowel evacuation, while not essential, is encouraged by the frequent feedings, the drinking of sufficient water, the addition of yeast to the diet and the administration of mineral oil. General bodily rest is to be encouraged, although rest in bed is very rarely necessary. A suitable diet would be as follows.

Breakfast Milk, 8 ounces, with cream if desired

Cereal, 5 ounces, with milk or cream

Egg, 1 soft boiled or poached

Bread or toast with butter

Fruit juice (at end of meal)

Midmorning. Milk, 8 ounces (cream $\frac{1}{2}$ ounce, lactose, $\frac{1}{2}$ ounce, or cocoa may be added if desirable)

Always with crackers, toast, bread or cake

Luncheon: Milk 8 ounces

Baked or mashed potato or plain spaghetti

Egg, 1 soft boiled or poached, or cream cheese

Bread and butter

Pudding, custard, gelatin or ice cream

Midafternoon Same as midmorning
Supper Same as breakfast or luncheon
At bedtime and during night (every 2½ hours, if awake) Same as at midmorning
Olive oil, ½ ounce three times a day before meals
Liquid petrolatum, ½ ounce at bedtime
Water, 6 or 8 glasses per day

2. *The removal of the cause*, as discussed under the head of etiology, consists in the systematic and thorough eradication of all infective foci. Half-hearted removal of an abscessed tooth or infected tonsils is rarely sufficient. It is necessary to search for and remove all devitalized or impacted teeth, and root fragments, fillings or cysts remaining after extractions. Moderate pyorrhea may be kept under control by means of frequent scalings, but the ultimate cure of definite pyorrhea is extraction of the diseased teeth. Infected tonsils or tonsil remnants must be extirpated, and nasal, pharyngeal, sinus and ear infections must be eliminated. Such common sites of focal infection as the male and female genital tracts, the rectum and all other parts of the body must be expertly examined and thoroughly cleaned up. Failure to remove all infective foci, even though diet is strictly adhered to, will eventually result in recurrence of ulcer, although an exacerbation is undoubtedly hastened by dietetic indiscretions or nervous or physical strain. With the appearance of a new ulcer, complete check-up for neglected, recurrent or new foci must at once be instituted, and in our experience such foci are always found.

3. *The treatment of the complications* of ulcer includes the treatment of perforation, stenosis and hemorrhage.

Perforation requires operation as soon as the patient has rallied from his shock (usually within the first two or three hours) the additional shock of too early operation often being the cause of unnecessary mortality. Operation during the first six to twelve hours results in the lowest risk. If not operated upon after twenty-four hours most patients die. Closure of the perforation by suture and covering with omentum is usually the best procedure, additional operative interference, on account of the increased risk involved, being carried out only where an obstruction is present.

Stenosis, whether due to hour-glass constriction or to pyloric or post-pyloric ulcer, also requires operation, but where the patient is depleted and dehydrated from prolonged vomiting a few days or even a week of preparation is worth while, reducing mortality and shortening convalescence. Such preparation would consist of frequent, small, liquid, concentrated feedings, subcutaneous and intravenous administration of chlorides and glucose and transfusions. Early feedings after operation and a proper dietetic régime afterwards, insure a good result. In the present article a discussion of the operative procedures is not desirable, but suffice it to say that the more simple the operation, the better it will be for the patient.

Gross hemorrhage is accompanied by shock and dehydration and is followed by a more or less severe anemia. Its treatment, which I have discussed in detail in a previous communication* involves the following principles

*The treatment of gastric hemorrhage, Jr. Am Med Assoc, 1927, lxxxix, 1397-1400

1 The promotion of blood clotting in the bleeding vessel; 2 The preservation of the clot when formed; 3 Treatment of shock; 4 Keeping the patient in the best possible general condition; and 5, Determining the nature of the lesion from which the hemorrhage originated. The first indication is absolute rest in bed, enforced by definite doses of morphine. This treatment combats shock and helps to check bleeding. Even though blood coagulation tests show normal findings, it is often best to use some form of medication to promote coagulation—horse serum, fresh or dried, thromboplastin preparations or whole human blood. A sudden increase in blood volume or blood pressure might tend to dislodge an early and unorganized thrombus, so that intravenous, subcutaneous or rectal fluids, and stimulants tending to raise blood pressure, should be avoided. In the presence of air hunger, transfusion of blood should be resorted to, but a small amount (250 cc or less) will usually be sufficient. After ten days, one or more larger transfusions will materially shorten the period of convalescence. Feedings are instituted at once in order to prevent the sometimes violent hunger contractions, which so often are the cause of recurrent hemorrhage. The food should be soothing, should promote coagulation of blood at the bleeding point, should combine readily with gastric juice (to prevent digestion of the thrombus) and should not over-stimu-

late gastric secretion. Such a substance is gelatin, which is used in solution and to which later are added gruel and milk mixtures, cereals, puddings, soft eggs, etc., until a regular ulcer diet is reached at the eighth or ninth day after treatment. Complete gastrointestinal study is not begun until nearly two weeks after the hemorrhage. Ice should be avoided, internally because it produces hyperemia of the gastric wall, externally because it adds to shock.

SUMMARY

1. So-called peptic ulcers are produced by the breaking down of areas of focal necrosis in the stomach wall, at varying depths below the mucosa.

2. They are the result of focal infection, the mechanism of their production being probably not direct infection, but some allergic or electrochemical reaction in the tissues involved.

3. They tend to heal spontaneously, each attack of ulcer symptoms being due to the development of a new ulcer.

4. The symptoms of ulcer are due to exaggerated hunger contractions and to retrostalsis.

5. The diagnosis of ulcer depends on history, roentgen ray and fractional gastric analysis.

6. The treatment of uncomplicated ulcer consists of diet and the thorough eradication of all focal infections.

7. Operative treatment is reserved for the complications of ulcer.

Malignant Melanoma with Delayed Metastatic Growths*

By DWIGHT L. WILBUR, M.D., and HOWARD R. HARTMAN, M.D., F.A.C.P.,
Division of Medicine, The Mayo Clinic, Rochester, Minnesota

MALIGNANT melanoma, frequently termed melanosarcoma or melano-epithelioma, is one of the most malignant tumors encountered in man. In some instances, however, the body seems to possess unusual resistance to metastasis from these tumors and it may be years after the appearance or removal of the primary growth before sudden, rapid and overwhelming metastasis occurs. This type of growth should, therefore, lend itself well to the study of the mechanisms of metastasis of tumors and bodily resistance to tumor growth, were it possible, with present knowledge, to approach such a study. The established observations of the delay in metastasis of these tumors are exceedingly important, not only in the diagnosis of this rare disease, but also because the prognosis may not be completely favorable in any case regardless of the time elapsed after excision of the primary growth. The present study has been undertaken with the view of presenting the histories of selected cases to reemphasize these facts, and to record observations on the life history of the disease. There are few

conditions apparently so readily cured in certain cases by simple excision as is melano-epithelioma, only to recur many years later in a rapidly fatal form following an interval of perfect health.

Malignant melanomas have been found to arise in several different organs of the body. The most common site is the pigmented mole of the skin and following this, in order, the pigmented areas of the eye, the anus and the suprarenal glands; such tumors have been reported as arising in the meninges, rectum, ovary, gastro-intestinal tract, gallbladder and other organs. There is considerable dispute as to the cellular origin of this type of tumor. It was formerly believed to arise chiefly from mesoblastic tissue and this, with the spindle type of cell which is commonly observed, led to the term melanosarcoma, which is still used. Certain observers believe it arises from the melanin-bearing chromatophores which are so widely distributed in the animal kingdom, although more recent interpretations place its origin among the epithelial cell group. Although the latter is the most commonly accepted view Ewing has recently accepted the work of Mason which would indicate that these

*Submitted for publication February 20, 1931

tumors have their origin in nevus cells derived from and belonging to the end organs of peripheral sensory nerves. The cell form varies from spindle to round and, although most of these tumors are pigmented with melanin, occasionally nonpigmented melanoma is encountered.

The spread of these tumors may occur in three ways: by direct extension, by lymphatic vessels, and by the blood stream. Death within a month of onset has been recorded, but the usual duration of life, according to Coley and Hoguet, is two to three years. However, in certain cases in which there is definite resistance to metastasis, recurrence may not appear for as long as ten to thirty years after removal of the primary growth. The various modes of extension and the various types of metastatic growths will be illustrated by the case histories presented. Cases have been selected in which metastasis occurred after a period of at least five years after excision of the primary growth.

In each of the following three cases the primary growth occurred in a pigmented nevus of the skin and led to metastasis which did not become prominent until years later. At the time of examination these cases did not present the widespread metastasis which is the terminal stage of the disease.

CASE 1 A woman aged 43 years, registered at The Mayo Clinic in May, 1919, because of a tumor of the right thigh. Ten years prior to registration, a mole on the right thigh was accidentally irritated, following which it bled and later enlarged. Excision of the nevus was carried out at that time and the patient remained well until 1914, a year previous to coming to the clinic, when a brown area developed in the

scar and gradually increased in size. Six months later she noticed swollen nodes in the right groin. Shortly thereafter anorexia and weakness began.

In the region of the scar there was a pinkish flattened area 4 by 2.5 cm, and in the inguinal region were many enlarged lymph nodes. Biopsy of these nodes showed melano-epithelioma. The patient died after she returned home.

CASE 2 A woman, aged 48 years, came to the clinic in May, 1928, because of weakness of four years' duration. For fifteen years she had had a raised pigmented nevus on the left leg. Shortly after the appearance of the nevus it was cauterized, without recurrence, but six years later a tumor developed in the left groin, which remained unchanged for several years. Four years prior to registration the patient had severe menstrual hemorrhage at the time of the menopause and following this the tumor in the left groin continued to increase in size.

General examination was essentially negative save for a fixed, firm tumor, 3 by 5 cm, on the anteromesial surface of the left thigh. The patient refused biopsy and returned home. A diagnosis was made of metastatic melano-epithelioma of the left groin. The further course is unknown.

CASE 3 A woman, aged 61 years, registered at the clinic in April, 1917, because of a growth in the left temporal region, which had started as a small lump one year previously. It grew rapidly and was cauterized a month later, but the ulcer which developed on the lump failed to heal and increased in size. Tincture of iodine had been applied locally on several occasions. The growth had been enlarging rapidly and was rather painful.

On careful questioning the patient recalled that twelve or thirteen years previously she had had a brown mole burned off the cheek just below the site of the present growth, which was a raised, rather firm growth 5 cm in diameter, covered with blood crusts on the upper portion of the left cheek. Just below it was a similar area 2.5 cm in diameter. There were no palpable cervical nodes surrounding it. The pigmented

area was excised. The pathologic diagnosis was melano-epithelioma.

The patient returned in September, 1917, at which time there was a small ulcer 1.5 cm in diameter on the face, but no clinical or microscopic evidence of recurrence. She returned again in November, 1917, stating that her health had been good until six days previously, when she noted drooling of saliva from the left side of the mouth. Left hemiplegia and aphasia with some frontal headache and delirium, and then coma, rapidly developed. Death occurred two days later.

At necropsy there was a large healed scarred area on the left upper malar region with atrophy and scarring of the skin. There were several areas of metastatic growth in the lungs, and bronchopneumonia. Excessive hemorrhage had occurred in the left internal capsule of the brain, and into all the ventricles, with thrombosis of the left lateral sinus. Although it could not be definitely determined, there was some suspicion that a metastatic melano-epitheliomatous growth was present.

It should be pointed out that following excision of the primary growth local recurrence may or may not take place, and that if local recurrence is present it may occur immediately following excision and remain stationary for years, or it may not be present until years later at the time of widespread metastasis.

The four cases of the second group are illustrative of the presence of distant metastasis in the absence of local recurrence in the skin.

CASE 4 A woman, aged 42 years, came to the clinic in June, 1926, because of a lump in the right groin, of four months' duration. In 1920 she first noted rapid growth of a pigmented mole on the calf of the right leg. The following year, the mole, which had become 2.5 cm in diameter, was excised (elsewhere) and a diagnosis of sarcoma made. Because of this, the popliteal area was dissected out a few days later. She had no further trouble until February,

1926, when pain developed and a lump was noted in the right groin. There was some question as to whether the lump had grown during the succeeding months.

General examination disclosed a large irregular fixed mass in the right groin which seemed to extend into the right side of the pelvis, where a large firm mass could be palpated. The scars of the previous operation appeared normal. A diagnosis was made of metastatic melano-epithelioma, and the patient returned home following treatment by irradiation. The outcome is unknown.

CASE 5 A woman, aged 53 years, came to the clinic in March, 1927, because of frontal headaches of two months' duration. The pains radiated to the occipital region, and they were persistent and intense. Nausea and vomiting, and vomiting unaccompanied by nausea, occurred. The patient was drowsy and lethargic, with diminished vision and drooping of the left side of the face. Ten years previously a mole had been removed from the left side of the face, it had recurred several times and was removed each time. Two months preceding registration a small black tumor behind the left ear had been observed.

General examination disclosed moderate obesity, lethargy, nystagmus and paralysis of the left side of the face. There was a firm tumor, 1.5 by 1 cm, below the left ear. It was somewhat tender, and movable. Ophthalmologic studies revealed bilateral choked disks of 4 to 5 diopters each, with hemorrhages and exudates in the retina. The roentgenogram of the thorax was negative. Biopsy of the tumor below the left ear disclosed melano-epithelioma, and a diagnosis was made of brain tumor (metastatic) and melano-epithelioma in the left temporal region. The patient returned home. Further data as to the outcome are not available.

Case 5 presents several interesting points. First, it illustrates the persistence of the growth in spite of continued cauterization and yet the long delay before the resistance of the patient was lowered or the virulence of

the tumor raised to the point of metastasis. Second, it illustrates the advantage of biopsy of a suspicious cervical or cranial node in the presence of an obvious intracranial neoplasm, for it not only clinched the diagnosis in this case, but it saved the patient a needless exploratory operation as well. Third, it is an instance of the rare case in which the presenting symptom of the metastatic growth is that of an intracranial lesion, and it is probably the type of case in which intracranial metastasis will be fatal before widespread metastasis is evident.

CASE 6 A man, aged 35 years, first came to the clinic in May, 1929, because of migraine and chronic nervous exhaustion. He returned in March, 1930, because of numerous subcutaneous lumps which had appeared in October, 1929. There had been slight swelling of the right testis for a few months preceding this. About twelve firm, painless subcutaneous nodules were scattered over the torso, all of which had progressively increased in size. The patient had grown increasingly pale, lost 10 pounds in weight and had a dry hacking cough. Malignant melanoma was reported following biopsy of one of the tumors (elsewhere). There was a history also of removal of a nevus from the right calf in 1923 or 1924.

On general examination fatigue was apparent. Numerous subcutaneous dark nodules, 0.5 to 2 cm in diameter, were noted. On the inner side of the right calf there was a clean scar where the mole had been excised. The abdominal examination was negative, as was the roentgenogram of the thorax. A diagnosis was made of malignant melanoma with metastasis. The patient returned home, where he died three months later of generalized metastasis.

Among the interesting features of this case is the absence of evident local or regional recurrence of the melanoma ten years previously. This is unusual considering the fact that the

lesion originated in the skin, which practically always gives evidence of local recurrence or of metastasis to the regional lymph nodes. The only clinical evidence of metastasis in this instance was the subcutaneous nodes, and it should be mentioned that this patient had been subjected to careful examination ten months previously, at which time the nodes were absent.

CASE 7 A man, aged 33 years, first came to the clinic in 1920, at which time a pigmented nevus on the skin of the left deltoid area was excised. There had been some recent increase in the size of the nevus prior to its removal. Thereafter the patient continued in his usual good health save for occasional attacks of vague abdominal pains, the exact nature of which could not be determined. In June, 1930, he returned to the clinic complaining of pains of two months' duration in the lower part of the abdomen. The pains occurred several hours after meals, and were associated with backache, fatigue, and loss of 15 pounds in weight.

General examination was essentially negative, but laboratory tests revealed secondary anemia (10.2 gm hemoglobin for each 100 cc), and occult blood in the stools. Roentgenographic examination of the stomach disclosed a small polyp. At abdominal exploration multiple malignant polyps were found scattered throughout the small intestine, one of which had produced intussusception of the lower part of the ileum. The patient was unable to withstand the operation and at necropsy widespread metastasis of malignant melanoma was observed. Six cauliflower-like pedunculated and sessile growths were found in the right auricle of the heart, the largest 2.5 cm and the smallest 0.7 cm in diameter. In the lungs were numerous firm nodules 2 mm to 2 cm in diameter. Similar metastatic nodules were observed in the liver and spleen (one nodule). The stomach was dilated and presented a polyp on the posterior wall 7 cm from the pylorus. There were many small masses scattered throughout the duodenum, jejunum, and ileum, the largest of which measured 5 by

3 by 15 cm They occurred as sessile, pedunculated or ulcerating areas, greater in number high in the small bowel The colon and rectum were free of metastasis Microscopic study revealed pigmented epithelial tumor cells with both adenomatous and epitheliomatous formation, and the diagnosis was made of malignant melanomatosis with multiple metastasis

The remarkable features of this case were the misleading symptoms which the patient presented The gastro-intestinal symptoms were outstanding and there was no suggestion of malignant disease until the time of operation when the carcinomatous polyps were discovered It was the presence of intussusception which led to surgical interference A similar case of metastatic malignant melanoma and intussusception of the small intestine has been reported by Maxwell The presence of widespread metastasis to the heart, lungs, liver, spleen and stomach and small bowel revealed the hopelessness of the condition and yet it had been ten years since the excision of the primary growth

The last group, which comprises three cases in which the eye was the site of the primary melanomatous growth, is perhaps the most interesting and clinically the most startling of the series

CASE 8 A man, aged 43 years, came to the clinic in June, 1930, because of weakness and an abdominal mass of six months' duration Seven months previously he had had a heavy cold with slight fever and thereafter he continued to have bouts of mild fever, malaise, pains in the joints and weakness Four months previously he first noted a painless, somewhat movable mass in the right upper abdominal quadrant which later enlarged and moved toward the median line Because of a sense of fullness the appetite failed, although there was no indigestion or

jaundice Further questioning brought out the fact that in 1916, fourteen years prior to registration, the left eye had been removed because of "acute glaucoma following detachment of the retina" and in 1929 he noted the appearance of dark colored nodules on the right wall of the thorax anteriorly, at the base of the neck, in the left axilla, the groin, and near the spine These areas were painless, movable, and had not changed in size during the last year

The patient was slightly emaciated and numerous firm movable black nodules were noted The abdomen presented a hard nodular mass with a definite border coming down to the umbilicus in the right upper quadrant, and the spleen was palpable A roentgenogram of the thorax disclosed an area of increased density in the right lower lobe, probably metastatic Tests of hepatic function disclosed dye retention graded 4, indicating marked hepatic disease Biopsy of one of the inguinal nodes was reported as melano-epithelioma The diagnosis was made of melano-epithelioma involving the liver and abdominal lymph nodes The patient returned home, where he died two months later

CASE 9 A man, aged 55 years, came to the clinic May 12, 1930, because of pain in the right upper quadrant of the abdomen and loss of weight He had been in his usual good health until six or eight months before admission, at which time illness which was called influenza by his physicians developed, with increasing weakness and gas on the stomach Although the respiratory infection rapidly cleared up, the feeling of abdominal distention became more pronounced and soon moderately severe continuous pain developed, starting in the epigastrium and passing to the umbilicus Two months before admission he had first noted the appearance of painless, subcutaneous lumps over the sternum and left shoulder About this same time the gastro-intestinal symptoms improved, but six weeks before admission a pressing pain developed beneath the right costal margin which bothered him, especially at night He had lost 20 pounds in weight. In general he felt well, with the exception of some weakness and slight cough with mucoid expectoration In 1920, his right eye had been enucleated because of a tumor

Biopsy of one of the subcutaneous nodules removed elsewhere had been diagnosed sarcoma

The patient was slightly emaciated. The orbit from which the right eye had been enucleated did not give evidence of recurrence of growth. There were numerous, scattered, firm, freely movable, painless, subcutaneous nodules over the scalp and thorax. The axillary and cervical lymph nodes were large and there was a large firm irregular mass, presumably the liver, in the right upper quadrant of the abdomen. A few râles were noted at the bases of the lungs. Laboratory studies showed mild secondary anemia with 126 gm of hemoglobin for each 100 c.c., and the roentgenogram of the thorax disclosed multiple metastatic granules. A diagnosis of multiple metastatic tumors throughout the body was made, the source undoubtedly being the tumor of the eye enucleated ten years previously.

CASE 10 A man, aged 53 years, came to the clinic November 18, 1930, because of stomach trouble which he had had for twenty years. The distress was a typical ulcer type of dyspepsia which became pronounced two months before admission. During this time he had suffered from constant epigastric pain which radiated to the right upper and lower abdominal quadrants and up into both sides of the thorax. Relief from food or alkalis was incomplete. There were no other gastro-intestinal symptoms and he had not lost weight. In 1920 the right eye had been enucleated on account of sarcoma of the eyeball.

The patient was emaciated. The tissues of the right orbit appeared normal. A small firm, freely movable, subcutaneous nodule had been present over the third thoracic vertebra for a year. A large, firm, irregular, scarcely movable and tender mass was palpated in the right upper abdominal quadrant; presumably it was the liver. Laboratory examination disclosed slight secondary anemia, the hemoglobin was 13.5 gm. Roentgenograms of the stomach disclosed an extrinsic mass. A diagnosis of melanoma of the liver was made.

The points of similarity of these three cases are quite remarkable. The

patients had all undergone enucleation of the eyeball for tumor (in the first case "detachment of the retina for glaucoma") ten or more years previously, apparently with success and with good health through the intervening period. In each case the presenting complaint was of epigastric pain focusing the attention on the abdomen, and on examination the liver was found to be large, firm, and irregular, obviously the seat of malignant disease. Each patient also presented one or more subcutaneous nodules, although there was no evidence of local recurrence within the orbit or of regional metastasis. The essential data of these cases are compiled in the tabulation (page 210).

COMMENT

Malignant melanomas arising within the pigmented nevus comprise the majority of such tumors. The various modes of metastasis have been illustrated in the case reports. There may be local recurrence of the growth following excision, metastatic involvement of the regional lymph nodes, or of neighboring organs, or widespread metastasis throughout the body.

The varying clinical picture observed in the localization of metastasis may be explained in four different ways: (1) it may depend on the occurrence of metastasis by way of the lymphatics, in which case transportation of cells by superficial lymphatics would lead to metastasis in the regional nodes, while transportation by deep lymphatics may lead to metastasis in more distant lymph nodes or even widespread dissemination through the thoracic duct and blood stream; (2) the metastasis may be by the hemato-

genous route, in which case widespread metastasis is more probable; (3) the clinical picture may depend on the stage, early or late, in which the disease is observed, and (4) the quality and quantity of metastasizing tumor cells may be the determining factors, as pointed out by Armstrong and Oertel, since with a small number of cells the localization depends on qualitative selection of suitable organs for extension of metastasis, while with large quantities of cells this qualitative restriction is overcome and widespread overwhelming metastasis occurs. At present, there is no method of predicting which means of dissemination will be followed by a melanotic tumor in a given case.

There is just as much variability in the time elapsing between the occurrence of malignant changes in the nevus and the development of disseminated metastasis as there is in the selectivity of routes of dissemination. The occurrence of these two factors is so well established that they need no further defense.

In each case cited there was growth of the pigmented nevus just prior to excision or cauterization. Such a change therefore immediately justifies a guarded prognosis as to the occurrence of metastasis following removal of a growing nevus. The impression should not be obtained that dissemination is bound to occur once visible proliferation of the original nevus has begun, but the point to be emphasized is that one can never be absolutely certain, even after many years, that widespread metastasis will not occur. It would seem that the treatment of choice in such cases would be not only wide excision of the offending nevus

but of the regional lymph nodes and intervening lymphatic vessels as well, as emphasized by Handley. The occurrence of bleeding, ulceration or crusting of a pigmented nevus should always be taken as a serious warning and be followed by immediate excision, as already mentioned.

Malignant melanomas arising within the eye comprise about one third of the whole group of malignant melanomas and are generally regarded as taking origin in the choroid, ciliary process, iris and conjunctiva. The more recent work, however, seems to indicate that they arise in the pigmented layer of the retina. This confusion is the result chiefly of failure to observe early cases histologically. The mode of extension from the eye, according to Dawson, may be in three directions: (1) by direct extension, (2) by lymphatics to the cranium, or more rarely to the cervical nodes, and (3) by the blood stream, chiefly to the liver. Among the numerable cases in the literature in which metastasis has been delayed for many years following excision of the primary growth are those of Wilder, thirty-two years; Schilling, twenty years; Lawbaugh, seventeen years; Fisher and Box, fourteen years; and Hutchinson, Lilley, and Dobbertin, ten years. The syndrome is so well established that when one is confronted by a patient with a glass eye and a large abdomen or liver the suspicion should immediately be aroused that a malignant melanoma has metastasized, regardless of the number of years since enucleation of the globe. Malignant tumors within the eye are nearly always primary for, as Cordes and Horner have pointed out, metastatic tumors to the eye are

rare (seventy cases of metastatic carcinoma to the eye are reported in the literature, chiefly from the breast), and there are only four recorded cases of metastatic melanoma of the skin with metastasis to the eye. Such metastasis usually occurs in the uveal tract. Metastasis from one eye to the other seldom occurs; consequently a malignant melanoma of the eye can be regarded quite safely as primary in that organ. Such statements as those of Karsner that "the pigmented choroid tumor is extremely malignant and secondary foci or metastasis develops very early" cannot be accepted for all cases, as has been illustrated.

Malignant melanomas arising in other organs have not been cited in the present study because delay in metastasis from such tumors has not been observed, chiefly because the primary tumor is not viewed as readily as are those in the eye or skin. Although melanomas conceivably may arise wherever melanin-bearing cells occur, their occurrence primarily in the stomach or small intestine is questionable. The usual involvement of the liver and occasionally of the gastro-intestinal tract in the absence of a known primary growth has led to the belief that the primary tumor may be in these organs, particularly if the patient's history is unknown. The secondary tumor in the small intestine may have all the appearances of a primary growth, as occurred in one of the foregoing cases, and also in the case cited by Saphir. Saphir's experience led him to conclude: "Reports of primary melanotic tumors of the intestine should be regarded with suspicion."

Delay of metastasis is probably more correctly called delayed metastatic

growth, for it is logical that the metastasis, or at least the dissemination of tumor cells, must take place before or during the successful operative removal of the primary growth. The mechanism of this phenomenon of delayed growth is not certain.

It is not difficult to understand the entrance into, and transportation of tumor cells by either the blood stream or lymph stream in the development of metastasis. Similar phenomena probably occur in the development of metastatic abscesses, foci of infection, or orchitis in mumps, and possibly also the so-called calcium metastasis in which this inorganic salt is carried from the bones to the lungs, stomach and kidneys. The development and growth of metastatic cells is so commonly observed that little attention is paid to the mechanisms by which they occur. It is this part of the development of metastasis which is so little understood. In this consideration Oertel stated "It must be appreciated that transportation of tumor cells and even arrest of tumor plugs are not identical with metastasis, for the conception of metastasis requires further a participation of the local tissues in the growth of cells to a tumor by furnishing the tumor cells with a vascularized stroma. The local susceptibility determines more than transportation of tumor cells the development of the metastasis."

The delay of metastasis must depend, therefore, not on any altered transportation of the tumor cells but on their delay in growth, and that this delay in growth may be for many years is a remarkable phenomenon. The actual transportation and distribution of the tumor cells must be very wide-

spread since the liver is so frequently involved secondarily. This would necessitate the passage of the cells through at least one or more capillary beds, probably two, that is, the pulmonary and portal.

The inhibition of growth of the transported tumor cells in certain organs over many years is evidence, perhaps, of failure of adequate powers of resistance of the organ or of the presence of an aggressive "formative irritant" (Oertel) in the tumor cells in their relation to the affected organ. Cohnheim stated "Only when and where tissues are lowered in their physiological metabolism by age, atrophy and inflammation will metastasis be possible." This would indicate that the resistance of the organ must be lowered before actual metastatic growth occurs and this may in fact be due, as Symmers put it, to some alteration in the "equilibrium of function in the cell (tumor) itself" or possibly to the occurrence of trauma. When such a point is reached the organ is stimulated to the development of a "vascularized stroma" and the growth of the cell deposit occurs with fulfillment of the conception of metastasis. Such hypothetic considerations will be replaced in time by more accurate facts as our knowledge increases, but for the present we are uncertain what influences suddenly fan the coals to flames when the metastatic growths appear.

It should not be supposed that malignant melanomas comprise the only group of tumors in which delay of metastasis occurs. Other types of tumor may show the same phenomenon and because of this the "three-year or five-year cures" of malignant tumors can not always be accepted. This is par-

ticularly well illustrated by such a case as that reported by Stacy and Vanzant in which an apparently inoperable carcinoma of the uterine cervix treated by radium seemed to heal and yet seven years later at necropsy metastasis in neighboring lymph nodes showed evidence of apparently recent, active carcinomatous growth.

There are several other points of clinical interest. The primary growth in malignant melanoma, unless it is within the eye or the brain, is not usually of great clinical significance. It is the widespread dissemination which usually destroys life, and death does not occur until widespread metastasis has occurred. This property applies to few other known tumors. McWhorter and Cloud found that in the nine cases of malignant melanoma which came to necropsy at the Bellevue Hospital widespread metastasis was present in each case and the liver was usually affected. Metastasis to the liver is present in the end stage in almost every case of this disease. This is an interesting phenomenon which cannot be explained at the present time except by the lowered resistance of the liver. Lymph nodes are not necessarily involved in every case.

The subcutaneous nodules observed as metastases may readily be misinterpreted as sebaceous cysts, as actually happened in one of the cases reported here.

From the medicolegal standpoint the delay of metastasis of these tumors may be very important, for the removal of the primary growth may occur in a period either covered or not covered by clauses in insurance policies or other legal papers, whereas the metastatic growth may occur years la-

SUMMARY OF CASES

Case	Sex and age	Primary Growth		Site of Metastasis	Appearance of Metastasis, years	Diagnosis	Chief Complaint	Outcome
		Site	Treatment					
1	11F	Mole on anterior surface of thigh	Excision	In scar and inguinal nodes	8.5	Biopsy of nodes	Tumor of thigh for six months	Died; time?
2	12F	Mole on calf of right leg	Excision	Inguinal nodes and pelvis	5	Biopsy of original tumor	Lump in right groin for four months	Unknown
3	18F	Mole on left thigh	Cautery	Anterior surface of left thigh	6	Clinical history and examination	Weakness for four years	Unknown
4	61F	Skin of cheek	Cauterization	Local recurrence and lungs and intracranial sinuses	12	Postmortem examination	Lump on face for one year	Died seven months after excision
5	53F	Mole on left side of face	Removed; several recurrences	Bram and behind left ear	10	Biopsy of mass on left ear	Headaches for two months	Unknown
6	35M	Mole on right calf	Excision	Subcutaneously, right tonsil	6	Biopsy of subcutaneous nodes	Subcutaneous nodes for five months	Died nine months after secondary metastasis
7	33M	Nevus on left arm	Excision	Heart; spleen, stomach, intestines, mesentery, lymph nodes; liver and lungs	10	Postmortem examination	Weakness and lower abdominal pain for two months	Died after operation
8	13M	Eye	Enucleation	Liver and subcutaneously	13	Biopsy of inguinal node	Weakness and mass in abdomen for six months	Died two months later
9	53M	Eye	Enucleation	Liver and subcutaneously	10	Microscopic examination of original tumor	Indigestion; abdominal pain for six months	Unknown
10	55M	Eye	Enucleation	Liver; lungs; bones, and subcutaneously	10	Biopsy elsewhere, sarcoma	Subcutaneous and abdominal tumors for two months	Unknown

ter under different legal conditions. The knowledge of delayed metastasis of malignant melanomas may be of prime importance under such circumstances

The treatment of malignant melanomas is unsatisfactory, they show practically no response to any type of irradiation therapy

SUMMARY

Ten cases of malignant melanoma arising in the skin and the eye with removal of the primary growth followed by delayed metastasis over periods of five to thirteen years are recorded.

These tumors recur and metastasize in various ways by local recurrence, by metastasis to the regional or distant lymph nodes, by widespread metastasis throughout the body, especially to the liver, or by a combination of these. It is the dissemination of metastases and not the primary growth which leads to death.

A conception is presented of the mechanism of delay in growth of the metastatic areas.

Studies of these cases reveal the value of the long-time study of a given disease in an individual case so as to become familiar with the complete life cycle of the disease.

BIBLIOGRAPHY

- 1 ARMSTRONG Quoted by Pepper
- 2 COHNHEIM Quoted by Pepper
- 3 COLEY, W B, and HOUQUER, J P Melanotic cancer with a report of 91 cases, *Ann Surg*, 1916, lxiv, 206-241
- 4 CORDES, F C, and HORNER, W D Metastatic melanoma of both eyes report of case, *Jr Am Med Assoc*, 1930, xcv, 655-658
- 5 DAWSON, J W The melanomata, their morphology and histogenesis, a study of cell origins and transformations with a critical discussion on aspects of tumor growth and a clinical review, *Edinburgh Med Jr*, 1925, xxxii, 501-732
- 6 DOBBERTIN Melanosarkom des Kleinhirns und Rückenmarks, *Beitr z path Anat u z allg Path*, 1900, xxviii, 52-56
- 7 EWING, JAMES The problems of melanoma, *Brit Med Jr*, 1930, ii, 852-856
- 8 FISHER, HERBERT, and BOX, C R Pigmented tumour of the eyeball death from multiple pigmented carcinoma nearly fourteen years after excision of the eye, *Brit Med Jr*, 1900, i, 639-640
- 9 HANDLEY, W S The pathology of melanotic growths in relation to their operative treatment, *Lancet*, 1907, i, 927-933, 996-1003
- 10 HUTCHINSON, JONATHAN, Jr Quoted by Schroeder
- 11 LAUROBAUGH Quoted by Schroeder
- 12 LILLEY, C H Quoted by Schroeder
- 13 MASSON Quoted by Ewing
- 14 MAXWELL, W Secondary melanomata of small intestine with chronic intestinal obstruction and intussusception, *Med Jr Australia*, 1928, ii, 656-657
- 15 MCWHORTER, J E, and CLOUD, A W Malignant tumors and their metastases, *Ann Surg*, 1930, xcii, 434-443
- 16 OERTEL, HORST Outlines of pathology in its historical, philosophical, and scientific foundations, 1927, Ed. 1, Montreal, Renouf Publishing Co, 479 pp
- 17 OERTEL, HORST Quoted by Pepper
- 18 PEPPER, O H P Metastasis, *Internat. Clin.*, 1924, ii, 269-286
- 19 SAPHIR, OTTO Metastatic melanoma of the jejunum report of a case, *Arch Path and Lab Med*, 1927, iv, 22-25
- 20 SCHROEDER, M J Late metastasis of melanosarcoma of the liver, *Med Jr and Rec*, 1924, cxix, 601-603
- 21 STACY, LEDA J, and VANZANT, FRANCES R Poisoning from cinchophen. *Minnesota Med*, 1930, xiii, 327-328
- 22 SYMMERS Quoted by Pepper
- 23 WILDER, W H Quoted by Schroeder

The Hospital

Its Relation to the Community and to the Medical Profession*

By WINFORD H. SMITH, M D, *Baltimore, Md*

IN the aggregate, the operation of the hospitals of the United States falls in the class of Big Business. With less than one thousand hospitals fifty years ago, we now have 7,000 hospitals in the United States. The value** of the hospital plants is about three billion dollars. The annual cost of maintenance is about 900 million dollars. The amount spent for new construction each year is 200 million dollars. The hospitals provide over 900,000 beds, in which every day there are over 700,000 patients. There are over 650,000 persons*** employed in operating hospitals, not including doctors and nurses. These hospitals treat about 12,000,000 patients each year. Further elaboration is unnecessary before this audience. I ask you to keep this picture in mind, however, with reference to topics which I shall discuss later.

Time would not permit a full discussion of all phases of the subject assigned to me. Therefore, I shall con-

fine myself to a discussion of some mooted questions. That there are such questions you well know. One has only to think of the numerous articles, by both medical and lay writers which have appeared in magazines and daily papers during the past few years, to be convinced, not only that there are questions requiring answers, but that there exist both general interest in and general lack of accurate information concerning most points under discussion. These articles deal with the cost of hospital service, doctors' fees, nurses' fees, the amount of free work done both by hospitals and doctors, in fact, they constitute a general discussion of the cost of medical care.

Doctors criticise (a) the cost of hospital service, particularly to private patients, (b) the cost of nursing service; (c) the amount of out-patient service; (d) the creation of diagnostic clinics, (e) the lack of accommodations for people of moderate means, and (f) the closed staff organization.

The question of costs will be discussed later. With reference to Out-Patient Service, there is no doubt that this phase of work has been much extended in recent years. There are now 5,000 dispensaries for poor people. These have been established to meet a

*Read at the Baltimore Meeting of the American College of Physicians, March 24, 1911.

**Estimated. The Public's Investment in Hospitals.

***Estimated. Personnel-Positions of the Hospitals in the Cost of Medical Care.

real need in the communities served and have, in most instances, been sanctioned, if not, recommended, by the staff members or medical boards of the hospitals. Rarely have such enterprises been undertaken by trustees or hospital managers independently of the staff. Can any one doubt the need of such services? Not if one were familiar with the types, and the large number, of patients flocking to the dispensaries.

Much has been said about dispensary abuse by patients. Repeated investigations have shown that such abuse is at a minimum, rarely, if ever, over two per cent. This would seem very low, probably no greater than the abuse of doctors' private offices. On the other hand, the hospital is criticised, if its officers attempt to check carefully the claims of the patient for free treatment or treatment at a low fee and if patients are admitted free. The same criticism applies to the admission of in-patients. In other words, the hospital is damned both ways. I believe it not only right, but desirable, that patients should be made to pay something, if possible. To make it too easy to obtain free treatment would be bad from every point of view, both for the patient and the doctor. Furthermore, comparatively few persons will choose a dispensary service except for the sole reason that they cannot afford to pay for the service elsewhere.

Patients are often admitted to dispensaries who pay a fee equal to that charged in some private offices. This is criticised. This does not occur often enough to offer any real competition and in most instances, this initial fee is seldom repeated, although the pa-

tient returns repeatedly for further treatment. It would be unsound practice to send such a patient away only to return later for continued treatment. There are many faults in our system, but they are not confined alone to the hospital or dispensary.

Recently articles have appeared berating the system which depends upon the gratuitous service of physicians. One writer suggested that physicians might organize and refuse to serve on the staff of any hospital or dispensary unless paid. I am sure that such a suggestion would be condemned promptly by the profession as unwarrantable and foolish, certainly it would be condemned by all who gave serious consideration to our system of hospitalization and its support. Of this I shall speak later. It is undoubtedly asking a great deal of busy doctors to give their service to the operation of dispensaries. On the other hand, many physicians have found it instructive and helpful in building up their experience which, particularly to the young man and the internist, is his greatest asset. The same is true to an even greater degree of the service rendered in the care of patients in the public wards of hospitals. Under the present system, the man who obtains a staff appointment, which calls for some of his time in caring for ward patients, receives quite as much as he gives, except, perhaps, those who have long since become well established and no longer need the hospital service for the experience and the prestige which such a connection undoubtedly gives. It is obvious that until a more stable basis of hospital support is found, hospitals will not be able to pay physicians

for services to the poor in the public wards and dispensaries

The development of diagnostic clinics for people of moderate means is not at present a great menace to medical practitioners, but it may be a factor of considerable importance in the future, unless the medical profession finds some other way of satisfying public demand. Undoubtedly, in the present era of specialization, people of moderate means feel that they simply cannot face the bill, resulting from being referred from one specialist to another, and some other system must be devised. Perhaps more well trained general practitioners will be the answer, perhaps group practice, as advocated by many, will be the answer. But if the latter, it must be on a basis of an inclusive fee, not separate fees of individual men merely grouped together for convenience and for cutting down overhead. In any event, the medical profession should find the solution, not the hospital, not the state, not the public health administrator; although, possibly, all should cooperate. However, some, or all, of these agencies will attempt the solution independently unless doctors attend to the safeguarding of their own field.

That hospitals have, in the past, paid too little attention to the provision of accommodations for people of moderate means is undoubtedly true. Such is likely to happen in the rapid expansion of any system, particularly if as haphazard as that of hospital development in this country. We concentrated first on the care of the poor; next came the provision of accommodations for the well to do. The reasons are ob-

It was necessary to provide for the poor because in no other way could they obtain proper care. The development of more complicated methods of diagnosis and treatment, and particularly the developments of surgery, made it desirable to provide at least the same opportunities of service for those who could pay as for those who could not. Furthermore, it has been the theory that by carrying a goodly number of private patients who could pay well for their accommodations, the overhead would be so distributed as to make it possible to render service to a larger number of poor persons. In more recent years it must be admitted that, in many hospital developments, perhaps undue attention has been given to the private patient class, particularly where those developments have been financed by general public subscription. Here it must be admitted that perhaps doctors have a right to criticize, because it has not infrequently happened that the public probably provided the funds under some misconception. It has been universal practice in campaigns for funds to emphasize the service to be rendered to the community, implying, at least, service to the poor and unfortunate. In reality, such movements have often resulted in the building of hospitals from funds raised by popular subscription which were very largely for private patients and for the benefit of a comparatively small group of doctors. Those doctors on the outside have had ground for criticism. Had the campaign literature or pronouncements stated frankly that so many beds would be provided; that most of them, the exact number being stated, would be for private patients;

that only staff members, would have the privileges, their names being given, no criticism would have been justified. But such campaigns have seldom been run on such straightforward and businesslike lines.

In recent years more attention has been paid to the people of moderate means. Hospitals are now attempting to provide this class with suitable accommodations at rates within their means. That this service has been lagging is not alone the fault of hospital trustees and administrators. We are all at fault. But some questions remain to be answered. Can such accommodations be provided at rates which will make the service self-supporting or must such a service be endowed? No definite answer which can apply generally has yet been found. Such a service can be made self-supporting in some localities, but, in determining where and how, we must consider the type of service to be rendered, the community to be served, the type of building required, the restrictions of the building code, and so on.

In large urban centers, where fire proof construction is demanded and where the most complex type of medical and surgical service is demanded, this question has not yet been answered satisfactorily. Boards of trustees are often faced with the situation that funds at their disposal have been given for charitable purposes and may not be used for this purpose. Therefore, unless self-supporting, endowment funds must be obtained. If a building is required, that means additional funds for that purpose. The Massachusetts General Hospital in Boston has embarked in this field in

a manner which should shed much light on the subject. It is important to know that the authorities of this institution decided, after careful consideration, that a building accommodating 300 patients represented the right sized unit which would offer a chance of operation on a self-supporting basis. An initial gift of \$1,000,000 was supplemented by other funds, bringing the total to about \$2,000,000 for the building. One of the large foundations promised \$150,000 to help offset any deficit for the first three years of operation. The prices range from \$4.50 per day for a bed in a nine bed ward to \$6.50 per day in single rooms. There are extras for operating room, x-ray, laboratory fee, etc. This unit, known as the Baker Memorial, has been open not quite a year and it is too early to know exactly how this experiment will work. It is significant that the authorities have stated publicly that such an undertaking could not succeed without the cooperation of the medical staff, the members of which agreed in advance to limit their fees to the patients in this building.

The closed staff is also criticised by doctors. The limited, or so-called closed, staff is generally favored for several reasons. It is believed by many that a carefully selected staff, members being chosen because of demonstrated ability and a capacity to work in harmony with others, will result in a more workable unit, with the maximum of standardization in all procedures, and will result in better care of patients and more economical operation. I believe this has been demonstrated to be true. There can be no argument on the point that all doctors are not of

equal ability. Not all members of a closed staff are of equal ability, but if the principle is sound and its application is made solely on the ground of ability, then that staff should be composed of men competent for the work assigned to them, supplementing each other and forming the best type of a working organization.

The Trustees must be satisfied that members of the Staff are competent and responsible, because in many states charitable hospitals are not liable for damages provided the governing boards have exercised due care in the selection of their officers and employees. It is also a fact that if poor work is done or glaring mistakes are made by a doctor in treating a patient in a hospital, the reputation of the institution suffers quite as much as that of the doctor concerned.

The point has been made that all public or community hospitals should be open to any reputable physician or surgeon in that community, arguing that only in this way will the general level of practice be kept on a high plane. That is yet to be demonstrated. On the other hand, I believe that if such a system were followed, those hospitals would not be as efficient in operation, nor as productive in developing outstanding men, nor in clinical and laboratory investigation, as under the restricted staff type of organization. Human nature is such that no matter what organization is adopted, even if all doctors were accorded hospital privileges, a considerable number, because of personal characteristics, environment, background, or general inaptitude, would always remain in the way of the best. In any event, the

welfare of the patient is the first consideration.

We must admit that the public at large has a definite interest, often a vested interest, in the welfare of hospitals. Yet the public is not well informed and, in consequence, is unduly critical. It is perhaps our fault that the public is not better informed. Some of the misinformation or lack of information is due to the manner in which appeals for funds are made, a point which I have already touched upon. Then, the public's advisors, as represented by the medical profession, are not always well informed because they are too busy to give careful thought to the subject and sometimes these same advisors are too ready to agree with the public. It is always open season for hospitals. It seems to me a very short sighted policy on the part of physicians, to criticise, as so often happens, without any constructive effort, those institutions which mean so much to the profession by way of the opportunities provided for their convenience and which are absolutely essential for much of their work. These men with hospital privileges have provided for them, and without cost to them, more facilities than are provided for any other professional group.

The public is critical of the cost of operation, resulting in numerous appeals for funds and high charges to patients, and because patients are sometimes turned away. The last point is often played up by newspapers. It should be obvious that a hospital, like any other building, has limited capacity, and even an urgent case must at times be referred elsewhere.

Furthermore, why should a hospital be expected to do more than its finances permit? In this period of unemployment, hospitals have been hit hard because of the increased number of patients unable to pay. For the most part, they have assumed the extra burden without assurance of additional funds. It is expected that hospitals will do this humane work. Are hotels expected to feed the hungry, do railroads and street cars transport the poor and unemployed free of charge, and do stores supply the necessities of life to these people without cost? Certainly not, no one expects it. But hospitals are expected to assume the burden on the theory that the public supports them. All would be fine if this were true.

Hospitals are expensive institutions to operate, much more so than twenty years ago. Why? For the same reason that the cost of living is much higher. The character of hospital service is much more thorough, more efficient, and more complex than formerly. The quarters provided have been made increasingly more elaborate, more comfortable, and are provided with equipment for efficient service far beyond the provisions of earlier years. Any medical man familiar with hospitals will concede these points without debate.

To be more specific, all articles of food and supplies of all kinds, cost much more. The old system of hard, soft, and liquid diets is no longer sufficient. We must have well organized dietetic departments which will provide diets of many kinds and varieties; cardiac, nephritic, diabetic, high calorie, low calorie, salt free, high protein,

low protein, and so on. This involves not only a constantly greater variety of articles to be prepared, some unduly expensive, but also infinitely more labor in preparation and service.

The service is much more complex, as exemplified in the greater care with which patients are studied, the more numerous tests employed, such as x-ray, fluoroscopic, basal metabolism, blood chemistry, bacteriological, serological, physiological, and biological. Treatment is also more complicated. More nursing service is required, larger resident staffs are needed, and likewise, more employees of all types. The modern hospital now requires a working personnel of about two persons for every patient and sometimes more. The planning of a hospital now provides smaller units for patients, the large open ward belongs to the past. This is necessary for the proper segregation of patients and their greater comfort. Hospitals cannot, and should not, rely entirely upon student nurses for nursing service as was the case in the past, with daily duty covering 12 or 14 hours. Shortening the working day for nurses, providing maids to do many of the household duties formerly assigned to the pupil, and the employment of more graduates, has increased the cost of operation enormously. The extensive developments of out-patient service, of social service, of follow up, of efficient record departments, provision for hydrotherapy, electrotherapy, light therapy, radium therapy, mechanotherapy, are all factors which have entered into the increased cost of hospital operation. They have all resulted from the demands of the profession because of increased knowl-

edge of disease and its treatment. No one should find fault with that

In discussing the attitude of the public towards the numerous appeals for funds we must all have some sympathy. We must go back to the basis upon which our hospital movement was conceived in order to explain the situation. In these days of super-efficiency, every enterprise not yielding a profit is under question. The vast majority of our hospitals are small, providing less than 125 beds each. They are financially handicapped to begin with, and must do considerable free work. Where can such hospitals obtain competent, well trained business managers? They are not available for such small institutions. These hospitals, therefore, for the most part, must rely upon nurses as managers. Have they been taught business management? No more than the doctors. A more conscientious group of workers it would be hard to find, most of them are overworked, are trying to do effective work for which they have never been trained, and are worried and harassed all the time. Sometime there will be a place where they can be trained specifically for such a job and then, perhaps, the job will be better done and they will command larger salaries and worry less. But I am sure that no more sincere and conscientious effort will go into their work. Until that time comes, however, these hospitals and their communities will have to be content and would do well to appreciate what they have.

Governing boards should know what the job demand, should know what qualification the persons possess

whom they select. If they are unable to obtain those who are thoroughly competent, they should help those whom they do select, not condemn them. Of course, changes are often needed, but those institutions which change managers every year or two frequently have something wrong with them other than the superintendent.

The larger hospitals, able to pay for competent service, are, I believe, for the most part, well managed. You cannot compare a hospital with an industrial plant with its well paid skilled labor and closely knit organization, all operating to the end that a standardized product shall be turned out as economically as possible, all costs being absorbed and a percentage added for profit. Hospitals are not engaged in that type of business. The hospital industry is engaged in mending broken bodies, in removing diseased tissue, in taking a machine which is out of order and causing it to function smoothly once more, and to continue functioning. No two problems are quite the same because no two individuals are quite the same, either physically or mentally. Furthermore, while we can and do carry business methods into every phase of hospital operation, there is a point where standardized procedure and business methods stop. That is where the doctor begins to function, in the professional care of patients. The doctor is successful because of his own individuality, his own method of doing the job, and his own personality. He is individualistic in his methods and it would be a sad day when the attempt was made to standardize him, if it were successful.

I referred to the basis upon which our hospital movement is founded. Has the growth of the hospital movement resulted from a carefully studied plan based upon the needs of the population? Have the 7,000 hospitals been established according to a definite program of so many beds per 1,000 population, so many beds for this branch of medicine, so many for that, based upon the needs of the communities to be served? You know that such is not the case. Is the movement the result of well established policies of the state for serving its citizens, such as the principle underlying our public school system? It has been a haphazard development depending for the most part upon the medical profession and groups of interested laymen and is based largely upon the principle that it is the duty and privilege of people of means to provide for their less fortunate neighbors. It is a beautiful principle and it has worked remarkably well, but is it sufficient to meet the requirements of the future?

The time has come when haphazard methods should be replaced by logical, sound methods based upon facts and sound principles.

To be more explicit, we have our Boards of Education which determine the number and type of schools needed, we have Chambers of Commerce, and Commissions for Industrial Development to look after the commercial interests of cities. Is it not equally important that we have some machinery to consider the hospital requirements? To be sure, we have our State and City Charity Departments and Health Departments, but considering the handicaps under which such departments operate, we would none of us wish to

place our hospitals under those agencies. I make the point that the time has come when there should be machinery of the State or the municipality which should concern itself with such questions as "Is another hospital needed, where, of what type, and how is it to be supported?" I do not mean that it shall run the hospitals. But such a commission should determine the needs of the community and should pass upon all new projects before they are undertaken and so long as our hospitals must depend largely upon public support, should determine how much of the expense should be borne by the State or its political subdivisions and how much by private philanthropy.

Of all the hospitals in the United States:*

- 49 per cent are of the private or corporate type,
- 26 per cent are federal, state, or municipal in type,
- 25 per cent are private or commercial in type.

We know that, generally speaking, the states and counties concern themselves principally with hospitals for the tuberculous and the insane. The cities provide some general hospital beds but not nearly enough. There are 5,600 community hospitals of which 4,300 are general hospitals. Generally speaking, excepting for the insane, the tuberculous and veterans in Federal Hospitals, the care of the sick poor rests largely with the corporate or community hospitals. Is this statement well founded? A recent survey** of the hospitals in Philadelphia

*Publications of the Committee on The Cost of Medical Care

**By Nathan Sinai, D.P.H., and Alden A. Mills, Committee on Cost of Medical Care.

disclosed that 40 per cent of all patients in all hospitals were free. In New York City, the 30 general hospitals participating in the proceeds of the United Hospital Fund provided, during the year 1929, 2,532,000 days of treatment, 44.2 per cent of which were free. These are certainly fairly typical of the situation in the east and perhaps to a lesser degree, in the west; where more general hospital beds are owned, and operated by the state and its subdivisions.

Who pays for this free work? The Survey in Philadelphia disclosed these figures for the 52 hospitals. Of the gross income available for operating these hospitals (excluding the Philadelphia General—a city institution)

- 58.7 per cent came from patients
- 16.5 per cent come from endowments
- 4.8 per cent came from cash contributions
- 9.5 per cent come from Federations
- 7.4 per cent come from public support—city

In other words, these hospitals did 40 per cent free work and received from public funds 7.4 per cent of their total revenue and had a total deficit aggregating \$355,779.00

I fancy this is quite typical of most cities varying, perhaps, slightly up or down. And yet, in most states, if not all, real estate owned by these private hospitals for purposes of revenue and even the endowment funds, the income of which is used for the poor, are taxed by both state and city and at the same rates as any other real estate or realty which may be owned and not for the profits of business or of a charity.

It is worth while to analyze the above figures somewhat further. About 43 per cent of the money available for operating these hospitals comes from sources other than payments of patients, and of this 43 per cent, only 7.4 per cent comes from public funds so that about 35 per cent comes from endowments, cash contributions, or the federations, which means, that in one way or another, this amount comes from private philanthropy.

It is significant that at this time, with the long history of the development of American hospitals back of us, the total endowment fund of hospitals is estimated to be \$437,000,000;* of which \$15,000,000 is for governmental, \$3,000,000 for proprietary, and \$419,000,000 for the community or non-profit hospitals. This amount of endowment for the non-profit hospitals is sufficient to fully endow 13,967 beds, of which there are 247,970 in this group of hospitals. The endowment is only sufficient, therefore, for 5.6 per cent of the beds. It is further significant, that of the 2,604 hospitals operating on the non-profit basis, only 1,060 control any endowments, and of this number, 125 hospitals control 45 per cent of the total, and only 31 of these control more than \$2,000,000 each. Many hospitals in the United States do not receive endowment income in sufficient quantities to materially affect their financial policies. The point of all this is that the system is not sound, that with the increased cost of hospital operation, it is doubtful if the present

*Figures supplied by Rorem in his book entitled "The Public's Investment in Hospitals."

system of support will prove adequate for the future

We certainly must not discourage private philanthropy, but would the system not be on a better basis if the burden were more equitably distributed by requiring the cities and states and counties to pay more nearly what it costs these hospitals for caring for the poor? It is stated that dependent persons are ill, on the average, nearly twice as often as persons with incomes considered adequate. The U S Children's Bureau,* in a study of 22,967 births, between the years 1911 and 1916, in eight cities, found that in families, where the earnings of the father were above \$1,250, there were 59 deaths per 1,000, that the number of deaths of infants increased per 1,000 the lower the earnings of the father for example, earnings \$850 to \$1,050, deaths 82.2, earnings \$650 to \$850, 107.5 deaths. Warner in American Charities gives illness as a cause of dependency in from 20.1 per cent to 43.7 per cent of dependent families. Considering these facts, would it not seem to be quite as important that we provide adequately from public funds for the care of the sick and for public health generally, as for education, for good roads, bridges, and harbors, all at public expense? Certain it is that until this or some other method is found, the public must expect appeals either separately or through community chests.

The public also protests against high charges in hospitals. In the 30 general hospitals in New York City, referred to above, the average daily

per capita cost was \$6.79. Generally speaking, we may say that the average per capita for general hospitals is probably at least \$6.00 per day. If the cost of public wards was distinctly separated, still the cost would be considerably more than the average charge in the public ward, which is generally about \$3 per day, rarely more than \$3.50. That does not seem high. To be sure there are extras, but for ward patients these are usually reduced to a minimum or remitted.

Private room rates are much higher, ranging in the more expensive types of service, from \$7.50 to \$15.00 per day, depending on size, location, with or without bath, etc. The average per capita cost for private room service is without doubt higher than the lower priced rooms, probably about the same as the average price charged for rooms. As a business proposition, this is not excessive, when one considers that the public will cheerfully pay the same price at a hotel and get much less for the money. In the hospital one receives, in addition to his room, three meals a day, some nursing care, services of the resident staff, orderlies, and maids, ordinary medication, surgical dressings, etc. To be sure, the extras are heavy in most hospitals. I think the principle of charging extras on a cost basis would be sound if credits were likewise offered where standard service is not used, but this would entail a complicated system of accounts and even hotels do not do that. Generally speaking, I believe it would be better to eliminate all extras, if practicable. Many hospitals have gone part of the way in this, but I do not think we can go all the way, in

*Frank J. Brewer, Hospital Social Work, Washington, D. C.

fairness to the average patient, who would thus be obliged to pay for the fads and fancies of the rich or cranky individual whose demands either directly, or indirectly through his physician, are often excessive. In determining the question of costs per day for private patients, it must be remembered that in most instances the buildings are given to the hospital and it is rare that hospitals include in operating costs any interest charge on capital invested or any allowance to be set aside to care for depreciation and obsolescence.

There is considerable criticism of the charges made by graduate nurses and of the need of employing graduate nurses in hospitals. I believe the charges of graduate nurses are not too high. They work long hours and must deal with situations which are most exacting, and sometimes, most unpleasant. They have periods of unemployment, sometimes long periods. The private duty nurse earns, on the average, between \$1,200 and \$1,300 per year, and her years of active service are limited. She is indispensable and her lot is hard, although satisfying from the standpoint of service. By comparison with other lines of employment open to educated women, her earnings are too small rather than excessive.

As to the complaint against the need of employing special nurses in hospitals, a survey was made by a national committee covering 1,892 private patients who had specials and this showed that in 40 per cent of the cases the doctor urged a special on account of special care needed, in 33 per cent the family wanted a special,

in 22 per cent the patient felt the regular service inadequate, in 3 per cent the hospital suggested one, and in 2 per cent the reason was that their friends always had one. I believe, however, that hospitals should provide more adequate nursing service, but they cannot do it under the present system.

The average duration of stay in the hospital, particularly for most surgical patients, is about half as long as was the case 25 years ago. This means that even if the hospital charge is double, the total hospital bill for that type of patient would be no greater than it was 25 years ago.

Considering all of these factors, I believe the charges are not out of line, although they seem high when the hospital bill, doctor's bill and special nursing fees are totaled. I believe the complaints rarely come from the man who can afford it, but generally from those less fortunate in this world's goods, which probably brings us again to the needs of those of moderate means.

Then, too, we must take into consideration that the average man has made no provision for illness. He resents illness anyway, and doubly resents the attendant expense. He has not denied himself in other respects, however. Wingate Johnson, in an article in the March "Atlantic Monthly" furnished these figures on the expenditures of the average family. He compares the cost of medical care with other items of the average family expenses per year:

For doctors	\$21
For medicine, chiefly patent	25
For hospitals	15

For nurses	8
For pleasure automobiles	150
For tobacco	67
For candy	37
For gasoline	37
For theaters	35
For soft drinks, ice cream, etc	34

In the study of the cost of medical care in Philadelphia, conducted by Nathan Sinai and Alden B Mills of the staff of The Committee on The Cost of Medical Care, the total bill for medical care is given as follows

Total cost			\$104,000,000
For physicians, dentists, nurses, and cults			47,000,000
Physicians	\$27,000,000	Principal items of the above figure	
For dentists	13,000,000		
For osteopaths, chirop, midwives, etc	3,000,000		
For patent medicines	obtained in drug stores		9,000,000
For prescriptions			7,340,000
For home remedies			3,692,000
For miscellaneous medical care sales			2,380,000
For hospitals, sanatoria, etc			16,000,000
For indirect costs not included in operating costs of hospitals			7,206,000
Some other minor items are not given here.			

The point is that the total cost of operating all of the hospitals is not the largest item by any means. The public spent for medical care sales in drug stores, a total of \$22,986,000, of which over \$13,000,000 was for patent medicines and home remedies.

But it is of little use to criticise the public because it spends so much for home remedies and patent medicine. While it is true that if there was less high pressure salesmanship and people spent less for radios, automobiles, electric refrigerators, electric washing machines, movies, etc., they would have more money with which to meet doctors' bills and hospital bills, finding fault will not remedy the evils of the situation. We shall doubtless face these same problems for a long time to come, but it is well to know the facts.

Many remedies have been suggested,

and among the most prominent have been

The formation of guilds for the purchase of medical and hospital service,

Health insurance, compulsory or voluntary,

State medicine

I am sure you have definite ideas on these subjects. The guild idea may be a good one; it sounds attractive, but in our present state of social development, and particularly in the larger

cities, I doubt if it would appeal to the class which presents the great hospital problem, the free and part pay patients. The same applies to insurance, unless compulsory, and therein lie dangers of many varieties.

In the very multiplicity of agencies and individuals concerned in the provision of medical care lies perhaps an outstanding weakness in our present system. It may well be that from the medical standpoint, the greatest need is not for more hospital beds, not for more doctors, or more public health activities, but is an agency for the organization and co-ordination of all medical facilities so that each may render its greatest usefulness to the public and may co-operate most effectively with all others in best serving the interests of those concerned in purchasing and paying for medical care.

The Profession and the Public*

By GEORGE EDWARD FOLLANSBEE,** M.D., *Cleveland, Ohio*

THERE are two points of view from which to look at medical economics, that of the profession and that of the public. The standpoint of the members of the medical profession has been consistently occupying the pages of state and other medical journals for years. The complaints and arguments of the doctors have been reiterated until you are familiar with them. The public has had its hearing in many popular magazines and weeklies and in the newspapers. The public never sees the medical journals presenting the complaints of the profession and few of the profession read any large proportion of the complaints of the public in the magazines. Neither side has a proper appreciation of the other.

I wish to bring to your attention some thoughts aroused by some of the more moderate criticisms by the public against our profession. In doing so I wish to be understood plainly as making no malicious charge against an honorable profession to which I am proud to belong. The spirit is rather

one of analysis and constructive criticism based upon the opinions formed about us by those who are not of us—an attempt to see ourselves as others see us, a wise thing to do at times.

The great cry is that it costs too much to be sick or to raise a family. I am not interested tonight in any cost except that of the doctor which approximates only about 25 per cent of the entire cost of health, sickness and reproduction. The impression has gained a strong hold on the better educated and more prosperous of the people that a general practitioner is not qualified to practice medicine; he might do as a distributor to direct to the proper specialist, or as a nurse, but that he is incompetent to actually take the responsibility of the care of illness, accident, childbirth or that latest entity, a healthy baby. So specialists are called and visited, clinics where routine methods multiply costs are sought in many trivial complaints, the costs rise and the medical profession is berated for excessive charges and accused of rank commercialism. It is unfortunately true that the profession is contaminated by some members who apparently took their oath to Mammion rather than to Hippocrates, but their number is small in comparison with that great body of men who always have and always will follow the

*Read at the Baltimore Meeting of the American College of Physicians, March 24, 1911.

**Formerly Journal Editor, American Medical Association; Member, Executive Committee, The Committee on the Costs of Medical Care.

ideals of the Hippocratic oath. We apologize to the public because of them. We do not defend them.

The number of self-styled specialists is ridiculous. It should be unlawful for a doctor to present himself as a specialist unless he has had adequate training and taken a degree in his specialty. That is something the medical profession of itself cannot accomplish but it can assist toward that end. Medical schools can revise their curricula as one step, teaching less of the intricacies of the specialties and more of the general course of preventive and curative practice which comprises seventy-five per cent of the family's needs, all of which can be cared for by a properly educated general practitioner. Much could be done toward this end by the thousands of open hospitals refusing their facilities to men for the care of cases which they are unqualified to treat. This is being successfully done today in some open hospitals with striking and convincing improvement in the mortality and morbidity rate, and lower costs to the people for hospital and funeral expenses. Also, the occasional specialist who gets much of his work from similarly unmoral colleagues is likely to overcharge for his services and be unprofessionally insistent upon collection. The temptation to pay commissions is likely to be beyond his power of resistance.

The statement that there are too many specialists applies to cities, especially the large ones, where most of the complaint of the high cost of medical care is made. It does not apply to towns and rural districts. Failing the correction of the rapid diminu-

tion in the number of general practitioners, of the excessive trend toward specialism, of the lawfulness of any or every doctor announcing himself to the people as a specialist, of the present almost prohibitive cost of some essential diagnostic procedures, of the commercializing of our profession by a small minority of its members, the excuse is valid for government and philanthropy and business to take over sections of practice, large or small, which should remain in the domain of private practice. The whole profession and particularly the real specialists should support the general practitioner and encourage the public to make all proper use of him. A specialist should return to the care of the referring physician all cases sent to him as soon as the need for special ability or special treatment is past. He should refuse to treat those cases coming to him over the head of a family physician when that physician could and would care for the case satisfactorily. It should be beneath the dignity of a specialist to care for such cases.

The older general practitioner is suffering from an inferiority complex. He is depressed and saying little, though he might say much, for he has seen the exceedingly rapid scientific advance of the practice of medicine with which he has been unable to keep pace. He realizes his limitations, but he does not realize that his years of experience have taught him an art of practice which will offset in many cases his lack of scientific knowledge, and of which his young competitor is ignorant.

The graduate of the last few years is quite competent to care for much

of the work that now goes directly to specialists and people should be taught so. We must re-establish the confidence in the general practitioner, the family physician; we must confine the work of the specialties to that requiring peculiar knowledge, ability or apparatus; we must practice medicine for the benefit of the people with financial gain honestly secondary in our thoughts, or inevitably the people with the assistance of private or public philanthropy will provide what we refuse to supply, medical care at a cost they are able to pay.

A very large proportion of whatever cost is excessive is due, not to the profession, but to the people themselves. This appears in the many instances in which people seek the services of the well known and most prominent specialists whose only way of restricting their work to their physical capacity is to charge fees commensurate with their reputation. It is evident in the demands by the people themselves for services of which they have heard but which in the particular case are not necessary for diagnosis or treatment. It is shown in the tendency of the public to look upon physiological pregnancy, child-birth and the rearing of children as a pathological process requiring the service of the specialist in all cases instead of only those with pathological complications. It is manifest in the habit of ignoring the general practitioner and primarily consulting some specialist when in the opinion of the patient is the proper one to treat the condition, only to find that the trouble is a local irritation of a condition not requiring the proper sphere of activity

To the extent that people themselves seek the services of a specialist for conditions which can be satisfactorily cared for by the general practitioner, they themselves are responsible for the excessive cost. Twenty to twenty-five per cent of them do not choose the right specialist in the beginning and so costs are pyramided.

These are matters for which we are only remotely responsible but which we should try to correct by education of the public, by advice and remonstrance to our patients, by recognition of the utility and ability of the general practitioner and by upholding the dignity and standing of the specialties by confining their work to conditions requiring expert ability and knowledge. We have a more direct responsibility in respect to those practices which are under the direct control of the members of the profession themselves.

Fault is found justly or unjustly with the practice of medicine in too many ways to consider all of them. The principle complaints are, (a) excessive charges for operations, (b) prohibitive expense of children, (c) unwarranted cost of diagnosis.

OPERATIVE COSTS

Excessive charges for operations refer of course only to the surgical specialties and complaint is made most directly and most frequently against general surgery.

There was a time not many years ago, when a specialist was a specialist by virtue of his superior ability and because the general practitioner expected to care for all the illnesses and accidents occurring in his clientele ex-

cept those of major severity. These he referred to a specialist if one was available. Graduates of those days were impressed with the dignity and exclusiveness of expert special work and had deep respect for the responsibility involved in major procedures.

As medical education and technique advanced, ideals as well as the training of the student changed. Specialties were divided on a basis of anatomic fields instead of personal ability. The idea grew that any condition occurring in an anatomic field belonged to that anatomic specialty. The change to this conception magnified the available field of the specialty to the student, minimized his comprehension of the knowledge and ability required and blunted his conscientious appreciation of his responsibility, until now the intention and expectation of the majority of graduating interns is to enter at once on the practice of a specialty in its entirety, usually general surgery, following general practice only so far as needed as a stepping stone to full specialization.

Many surgical procedures which formerly were considered major, by virtue of advancement in knowledge, technique and hospital routine are now essentially minor. The present graduate who has served his time as intern and resident is competent to perform many operations which formerly justly belonged to the surgical specialist. Should these men restrict their ambition to operate to those cases in which they are competent; should the surgical specialist admit the competency of these men in this limited field, should the public be educated to accept them for such opera-

tions, should these men themselves recognize that the operations which they are competent to perform are essentially minor and regulate their fees accordingly, much of the cry about the excessive charges for operations would be stilled. By recognition of this principle many would be satisfied to be general practitioners who now aspire to be specialists, and the hospital mortality and morbidity rate would be reduced. A recent survey of the physicians of two of our large cities shows that on the statements of the individual physicians themselves, twenty-eight per cent are complete specialists, thirty-seven per cent are partial specialists and only thirty-five per cent are general practitioners. The people cannot support a medical army with so many generals. There must be more privates. The effect of present medical education and professional aspiration has been to increase the field of the specialty and along with it the number of specialists, and as a necessary corollary has restricted the field for, and the number of, general practitioners. The opposite should occur.

The tendency of partial specialists to over-value their services has already been noticed. The code of ethics for years has declared that too low charges are unprofessional, on the basis of harm to the public. Too high charges are harmful though for a different reason and are equally unprofessional. This matter therefore is to a degree under the control of medical organization. In so far as this abuse exists and comes to the attention of medical organization, in self-preservation and devotion to professional ideals cogni-

zance should be taken, for the reputation of the whole profession is sullied by the reprehensible acts of comparatively few.

CHILDREN COSTS

The popular cry that the production of a family of children is too expensive now-a-days invites one to ponder the cause of such a condition. Some years ago the birth and raising of children was taken as a matter of course quite like the buying or building of a home. The greatest concern until the child entered school was the furnishing of food and clothing. It was all normal like other health. The confinement which turned out badly was looked upon as a "sickness" just as was any other departure from health. Today, how different! The human being from germinal cell to school age, in the popular attitude, is a pathological entity and the process of its being seems to be accepted as pathological throughout its course, except at its beginning. During the last ten years the act essential to impregnation has been transferred from the moral and spiritual field of contemplation and is now generally allocated to the purely physiological. On the contrary pregnancy, child-birth, infancy and childhood have been transferred from the physiological to the pathological field. Quite naturally, the result has been to increase cost. Green-houses tomatoes cost more to produce than field-grown ones.

The patient is not to decide all present and future specialists, but the general practitioner and pediatrician. They are the ones who are to be the first to be brought to the attention of the

grown up a mild national hysteria on reproduction which is involving the major portion of the populace wherever the various specialists can be found. Who started it and who keeps it alive, whether political public health or voluntary charitable agencies, the medical profession or the people themselves, will be answered according to the point of view of the individual answering. But whoever is responsible, the system has been over promoted. It is costing too much and we should return—not to the former status but to a common sense basis. What is there so profound or abstruse about prenatal work or raising normal babies that a general practitioner is incapable of giving satisfactory service? What expertness is needed in a normal confinement that requires a high priced specialist to be within call while an intern and obstetric nurse watch the progress of labor so as to call the obstetrician at the proper time to be present at the delivery?

The general practitioner is sufficiently well trained to do all a specialist does in a normal confinement, or should be if he is not. The field of the obstetrician and the pediatrician should be in the abnormal or unusual case, called in by the general practitioner when his skill is insufficient. Babies and children do cost too much under the present system but the system should be changed. Our part in the change individually and collectively, is to educate the people to "render unto Caesar the things that are Caesar's" and to teach the general practitioner to "render unto God those that are God's." Pressure should also be brought on medical colleges, if needed.

to educate the student sufficiently well in obstetrics and pediatrics to give all needed care to normal cases and be able to recognize those conditions which need knowledge and ability beyond his own. The public will be benefited. The general practitioner will be elevated to his proper dignity in the profession. The specialist will lose none of the work which properly should be his.

I have chosen to speak particularly of those specialties about which complaint is made most loudly by the layman. Critical examination of others would develop some justifiable cause and lead to corrective suggestion. Internal medicine while not yet subdivided to the same extent as surgery, is tending that way, much, I believe, to the detriment of both public and profession. And it has its weak spots.

DIAGNOSIS COSTS

I will conclude this critical, and I hope, constructive analysis by discussing the third feature calling down upon our heads the greatest amount of complaint, the unwarranted cost of diagnosis, a subject which involves us all. Diagnosis! The interesting case! It is the most attractive game in medical practice. It is to medicine as the mystery story is to literature. We all play it. We all are entranced with it. The autopsy or the operation proving our acumen is like the reading of the last pages of the story to test our accuracy of deduction. Without that last proof we are unsatisfied.

Tests in chemistry, bio-chemistry, physics and physiology have multiplied until we are bewildered by the signs, reactions, interpretations and

indications. And many of these cost money. Someone must pay. If the patient can he must, though the cost of scientific laboratory diagnosis may overshadow the other expenses connected with his illness. If all these are needed to make a diagnosis or direct his treatment he should pay for them. But many such expensive procedures are carried out which are not essential to correct diagnosis. They are the luxuries of medical practice. The rich want them and should have them. The man of restricted means may want them but he should not have them. They are sometimes ordered for the doctor's own satisfaction or to teach interns. Such a use is proper in the case of the rich or the free patient but is unwarrantable in the case of the ordinary pay patient. When a doctor orders examinations for which the patient must pay he is at the time the guardian of the patient, the trustee of his funds. Such meticulous care and sound judgment should be exercised as would be expected of a similar legal relationship. It is the doctor's duty even to remonstrate when the patient in his ignorance suggests or requests needless expensive examinations. There is no relationship requiring such a high grade of honor to exist as that between the patient who places his life and his pocketbook without redress in the keeping of a doctor and the doctor who accepts that trust. It is to the everlasting honor of the medical profession that that trust is so infrequently abused. It is more frequently abused in thoughtless enthusiasm than in willful violation, but the results are the same to the patient.

There is some justified complaint of routinely passing the patient around from one specialist to another because certain anatomic fields may be involved. Needless to say the same conscientious consideration should be exercised as in the ordering of laboratory examinations

The matters which have been brought to your attention are not amenable to change by organized medicine. The change in attitude by profession and public must come from the thoughtful sympathetic consideration, the conviction and the dictum of the scientific leaders of the profession, the members of the special societies. Through these influential men the public can be educated. Public opinion is the driving force which determines policies in this country. The medical profession is no less subject to it than is business or politics. With the help of the sensational, the propagandist and the welfare press a tide of public opinion inimical to the profession is rising which has already become a distinct menace. That the logical result of such opinion as is now being formed, will in the end be incalculably harmful to the people as

a whole will make no difference for the mass of the people do not think logically. The medical men themselves must do the thinking and the educating of the public. The first step in this education is to correct within the profession all justifiable complaints against the practice of medicine that are possible of correction. And all are possible of correction if the scientific leaders realizing the danger have the will to correct. Then we can come to the people with clean hands. Then with sincerity and conviction we can educate the public. Organized medicine has the machinery and the power of defense against adverse opinion but it cannot form public opinion and cannot ultimately prevail against a rising tide. Resolutions and articles in medical journals do not reach the layman and would be discredited if they did. It is only by public and private pronouncement by the scientific leaders, upheld by the influential men of the profession that the change can come. It is to you men of the special scientific societies that the profession must look for leadership.

Editorials

CINCHOPHEN POISONING A PARTIAL EXPLANATION FOR THE INCREASING INCIDENCE OF ACUTE YELLOW ATROPHY

Acute yellow atrophy of the liver is by no means the rare condition now that it was when it occurred almost solely as a disease of pregnancy and of the puerperium. Since then it has been shown that the toxic necrosis produced by chloroform, particularly in the condition known as delayed chloroform poisoning, is indistinguishable in its pathological features from acute yellow atrophy. That syphilis alone may produce marked changes in the liver parenchyma came to be generally accepted and in combination with arsenical therapy, syphilis was found to give the full clinical picture of acute yellow atrophy. In susceptible individuals arsenical drugs alone and in usual therapeutic doses were proved to be sufficient. In the munitions factories during the war and in industrial uses since, such substances as trinitrotoluene, trichlorethane and carbon tetrachloride have been found capable of producing extensive hepatocellular necrosis of this same general type. The parenchymatous lesion of phosphorus poisoning is distinctive in its early stage by reason of the diffuse fatty degenerative infiltration which it produces, but in the reparative stage it may be confused with the hepatitis produced by the other agents mentioned. Some have claimed that alco-

hol found in combination with other substances in home-distilled and synthetic beverages, is the cause of the increase in acute parenchymatous degenerative hepatitis of this type. Moreover, most of these livers now are not seen in the acute stage by the pathologist, but only when reparative changes are well established, with extensive bile duct proliferation as an attempt at liver regeneration. These are examples of what may well be termed subacute 'acute yellow atrophy' and chronic 'acute yellow atrophy'—a true toxic cirrhosis in a reparative phase. There is full proof that the cinchophen (phenylquinolinecarboxylic acid) group of drugs has had a share, how important can only be surmised, in increasing the incidence of acute yellow atrophy of the liver. Although 'atophan' was introduced in 1908, it was not until 1925 that the first report of a fatality from the use of this group of drugs appeared, but the occurrence of jaundice had been previously noted in numerous instances. Since 1926 the cases have multiplied rapidly. Within the last few months several excellent papers* have appeared giving evidence

*PARSONS, L., and HARDING, W. G., Cinchophen (atophan) poisoning, report of four cases, *Am Jr Med Sc*, 1931, clxxx, 115-125, SHERWOOD, K. K., and SHERWOOD, H. H., Acute toxic hepatitis (acute yellow atrophy) due to cinchophen, *Arch Int Med*, 1931, xliii, 82-88, BEAVER, D. C., and ROBERTSON, H. E., The specific character of toxic cirrhosis as observed in cinchophen poisoning, *Am Jr Path*, 1931, vii, 237-257.

of the widespread interest in this condition. Beaver and Robertson have reported five fatal cases from the Mayo Clinic and have described in detail the various stages of the liver injury and its attempted repair. Sherwood and Sherwood collected forty-eight cases from the literature and added one. From these cases they have built up a composite clinical picture which is exactly like that of acute yellow atrophy as formerly known. In some instances symptoms have arisen as late as ten days after the cessation of administration of the drug. At first there is nausea and gastric irritability followed shortly by the onset of jaundice, biluria and pruritis. The jaundice deepens and at this stage progressive decrease in the size of the liver can be demonstrated. By the third and fourth week, if the patient is not to recover, the jaundice and toxemia have increased and splenomegalia, ascites and edema of the extremities may develop. Finally the patient becomes delirious, and then comatose and dies. It appears that re-administration of the drug, even in small quantities, will usually produce a prompt return of jaundice. This indicates, then, that use of the cinchophen group is contraindicated in patients who give either by history or by clinical findings evidence of previous or present liver disease. Unfortunately, physicians are not always aware that various antirheumatic preparations, distributed under sundry trade names, belong to this group. Oxylindole, for instance, doxylodiphen and 11-hydroxy are all cinchophen drugs and they all of them have produced the same type of liver disease. A

predisposition or idiosyncrasy, dependent upon as yet unknown factors, seems to be significant in determining that an acute yellow atrophy will result.

SUICIDES IN THE UNITED STATES IN 1930

According to the compilation by Frederick L. Hoffman which appeared in *The Spectator* of May 14, 1931, there were 6,440 deaths by suicide in 99 American cities in 1930. This yields a death rate from this cause of 20.0 per 100,000, the highest figure since 1915. On the basis of these statistics it is believed that the annual loss of life by suicide in the Continental United States must reach 18,000 to 20,000. The nation-wide industrial and business depression has undoubtedly played a large part in the increase in the total number of suicides for the past year. From the medical standpoint the changing trend in the means chosen for self-inflicted death is of considerable interest. There are fashions and modes in suicide as in all other human activities. We have passed through a period in which much newspaper publicity was given to poisoning by bichloride of mercury and to various means for combatting that condition. As a result, there was an increase in the homicides in which mercurial compounds were the active agent. The suicide record for 1930 shows that jumping from high buildings and other high places is becoming an increasingly frequent method of self-destruction. In many cases it has been found impossible to determine whether death by this means was an accident or a suicide. There were 21

least two suicides recorded during the year of persons who jumped from airplanes while in flight. Extreme caution should be used in guarding high places in various ways, such as by protective devices, and in making it impossible to open the cockpit doors of airplanes except at the will of the operator or an attendant. The annually appearing statistical study of the suicide problem which Hoffman has prepared for so many years has done much to keep this question before the public eye. He properly insists that there is much that is remaining undone which would go far toward preventing this wastage of human life.

MORTALITY RATE FOR THE FIRST SIX MONTHS OF 1931

From various sources come reports that the first six months of the present year have been unusually healthy. Out of the tripartite combination of general business depression, closing hospitals and idle doctors, and general good health, has arisen the opportunity for the columnist and jokester to aim his thrusts at the medical man for it appears that it brings good health when people generally cannot afford medical attention. Others find the explanation in less extravagant living, plainer food and more hours of sleep. However, figures recently released by Dr. Henry F. Vaughan, Commissioner of Health, giving the mortality record for the City of Detroit for the first

six months of 1931 show very clearly that the reduction in mortality has involved such widely diverse diseases that economic factors alone cannot provide an adequate explanation. As compared with the first six months of 1930, deaths from tuberculosis decreased 20 per cent and the pneumonia death rate fell from 116.5 per 100,000 to 92.2 per 100,000. The death rate from diphtheria declined to less than one-half its former level and deaths from meningococcus meningitis decreased 77 per cent. Only deaths from cancer showed a slight increase, rising to 72.3 per 100,000 from 70.3 per 100,000. The rate for heart disease remained the same at 147 per 100,000. All important causes of death except the two last mentioned showed significant decreases. If this condition continues Detroit will have the lowest death rate in 1931 that that city has ever had. It is evident that the lowered mortality occurred throughout a wide range of infectious, and therefore preventable, diseases. In part, at least, hospital wards are poorly filled because there are fewer people ill, and the most important reason why there are fewer people ill in 1931 is that medicine is intrinsically altruistic. For the period reported upon, the death rate for typhoid fever for Detroit was but 37 per 100,000, approximately one in 300,000. As compared with conditions of fifty and sixty years ago the saving for health and life from this one disease will explain not a few empty hospital beds.

Abstracts

Traumatic Military Tuberculosis By JEAN FIRKET (Rev belge des Sci méd, 1931, III, 532-547)

Two illustrative cases furnish the basis for a discussion of the pathogenesis and medico-legal significance of military tuberculosis following trauma. In one instance a young man died 21 days after receiving a severe blow upon the head. At autopsy an active tuberculous meningitis with scattered military tubercles in lungs, spleen and kidneys was found. An old cascating focus was found at the hilus of the right lung. In the other case there was chemical trauma to the respiratory tract by the inhalation of ammonia. Death occurred 12 days later. Young military tubercles and early exudative foci were found in the lungs, spleen, kidneys and meninges. There was an old hilus lesion. It was decided that these two cases could properly be considered examples of traumatic military tuberculosis. It is suggested that the following points must be established before admitting a causal relation between trauma and the development of a military tuberculosis:

1. The reality of the accident,
2. That the clinical symptoms and particularly the fever did not appear until some days after the trauma,
3. That there were no clinical evidences of the development of a tuberculosis before the traumatism,
4. That the diagnosis of military tuberculosis was confirmed at autopsy, and the distribution of the lesions found to correspond with the clinical signs,
5. That a series of tests of recently active tubercles of tuberculous material was all successful.

BAUMANN and C. SCHILLING (Klin Wchnschr, 1931, x, 1249-1252)

The principle of contrast demonstration proposed by Radt and investigated also by Oka is the basis of the present study. In this method the contrast substance introduced in colloidal state into the organism parenterally, is taken up by the reticulo-endothelial cells in finely granular form. In further study of this method the authors made use of a preparation containing 25 per cent thorium dioxide (ThO_2) which was miscible with all body fluids without precipitation. It was found that 1 cc of this 25 per cent thorium dioxide preparation was sufficient to produce a positive shadow of liver and spleen in a 2 kgm. rabbit. The shadow reached its maximum depth in two hours. Through further injections and in larger amounts (3 cc twice a day until 12 cc had been given) a much deeper shadow resulted. Histological study of a few animals showed very fine glistening particles in the reticulo-endothelial cells. After twenty-four hours the Kupffer's cells of the liver were found greatly swollen and in a rabbit which had received 12 cc of the thorium preparation they were as large as liver cells fourteen days after the last injection. There was no necrosis of liver cells found. This method was made use of successfully in studying the effect of drugs upon the size of the spleen and liver in rabbits and dogs.

Studies in Asphyxia. I. Neuropathology Resulting from Comparatively Rapid Carbon Monoxide Asphyxia By JOHN CHORNEY and R. R. SAYRE (Public Health Reports, 1931, XLVI, 1523-1530)

It has been repeatedly observed that cases of carbon monoxide poisoning have a fatal termination even though respiration has been restored and the carbon monoxide removed from the blood. The series of experiments, of which this is the first report

have in view obtaining fundamental information as to the response of the animal organism to such an asphyxial environment, looking toward devising a therapeutic procedure for apparently moribund cases of carbon monoxide poisoning. This first study deals with the neuropathology found in four dogs after continuous exposures of 20 to 30 minutes to 0.6 per cent carbon monoxide by volume in air. These conditions produce 75 to 85 per cent carbon monoxide hemoglobin and result in death at the end of the period of exposure. The changes found in these animals were fairly constant and were lacking in control material. The brain, as a whole, showed a severe perivascular and perineuronal edema. This was most marked in the corpus striatum, the cortex, and the dorsal motor nucleus of the vagus nerve. Congestion was marked throughout and there were a few petechial hemorrhages in the corpus striatum and cortex. A few lymphocytes and leucocytes were found in the perivascular spaces. Many nerve cells were swollen, distorted and vacuolated and showed marked changes in the Nissl material. Some cells were shrunken and stained diffusely while others showed varying degrees of chromatolysis. The most serious lesion produced by this type of asphyxia appeared to be the edema of the dorsal motor nucleus of the vagus and the adjacent area in the medulla oblongata.

Insulin Resistant Diabetes By MARCEL LABBÉ (Rev. belge des Sci. méd., 1931, III, 465-491.)

Those paradoxical cases in which insulin fails to give the usual effects and which are spoken of as "insulin-resistant" appear to be frequent to some observers and rare to others. A majority of the published examples of insulin resistance represent errors in interpretation growing out of poor management in connection with insulin therapy. True insulin resistance exists but it is rare. It appears in an incomplete form in certain endocrine diabetics, and in a complete form in certain cases of insular diabetes without

any known explanation. Its existence may be established, (a) if in a diabetic on a suitable régime insulin fails to depress the level either of glycosuria or ketosis, (b) if in a diabetic who is adhering to a suitable régime excessive amounts of insulin are required to prevent glycosuria and acidosis, and to maintain nutritional equilibrium, or (c) if the sub-cutaneous or intravenous injection of insulin in the amount usually employed to demonstrate a hypoglycemia fails to lower the level of glycemia to the degree usually seen in the diabetic. Rigid application of these criteria will make it possible to exclude the false examples of insulin resistance and to recognize the true condition in both its incomplete and complete forms.

Effect on Life Insurance Mortality Rates of Rejection of Applicants on the Basis of Medical Examination By ROLLO H. BRITTON (Public Health Reports, 1931, XLVI, 46-62.)

In connection with a joint investigation on occupational mortality by the Actuarial Society of America and the Association of Life Insurance Medical Directors data were secured on ordinary insurance business during the years 1915 to 1926, involving more than one-half billion dollars in death claims. Analysis of this large mass of information suggests that the insurance medical examination results in a lower mortality during the earlier insurance years as compared with persons of the same age who have held policies for a longer time. The duration of this selective effect appears to last for three or four years for all causes, except possibly at the highest age levels. For tuberculosis and heart disease it is possible that the selective effect is of much longer duration. The mortality rates in the first years of policy life are only about two-thirds of those after the effect of selection has disappeared. These results would seem to have an important and positive bearing upon the question of the value of periodic health examinations.

Reviews

Physical Diagnosis. By WARREN P ELMER, B.S., M.D., Associate Professor of Clinical Medicine, Washington University, School of Medicine, Assistant Physician to Barnes Hospital, Physician-in-Charge Missouri Pacific Hospital; Consulting Physician to Jewish Hospital, St Louis and W D. ROSE, M.D., Late Associate Professor of Medicine in the University of Arkansas, Little Rock, Arkansas. 903 pages, 337 illustrations The C. V. Mosby Company, St Louis, Mo., 1930 Price \$10.00

This book is a very complete revision of the work by W. D. Ross on the same subject. There has been a rearrangement of the subject matter with a division between the technic and the findings in the physical examination of the normal body (Part I, 530 pages), and the physical diagnosis of disease (Part II, 338 pages). This difference may be clearly understood if Part I be thought of as General Physical Diagnosis in contrast to the Special Physical Diagnosis of Part II. Throughout the first division there are numerous references to pathologic conditions and the technic of eliciting those physical signs which are produced only in pathologic conditions is also included in this section. Of necessity, since this is a textbook suitable for use in medical schools, the level of approach is that of the second year medical student. Nevertheless the more advanced student, the intern, and the practitioner will find this book of very great value. The reviewer feels that it should not be necessary to include such information as that the heart has two auricles and a ventricle or that the left auricle and the left ventricle are connected by the mitral valve, which is a very common mistake in the first place. It is a pity that the book is so full of such errors, but it is a pity that it is so full of such errors.

lung as given (page 62) is less than one-half that known to exist at the present time. Taken as a whole, however, this is a very useful and very well written book. The illustrations are extremely well chosen. They show precisely how certain procedures are to be carried out. Surface relations are illustrated by both photographs and skeletal charts arranged in pairs in a very instructive manner. No opportunity is lost to teach clinical pathology on practically every page.

Selected Readings in the History of Physiology By JOHN FARQUHAR FULTON, M D, formerly Fellow of Magdalen College, Oxford, Sterling Professor of Physiology, Yale University. xx + 317 pages, 60 illustrations Charles C Thomas, Springfield, Ill, and Baltimore, Md, 1930 Price, \$5.00

This interesting work is a source book for the history of Physiology. Eighty-five selections have been chosen from original sources and are presented in the original English, if the text first appeared in that language. Otherwise contemporary English translations are used where such exist. Each is preceded by a brief explanatory note, in part biographical and in part indicating the significance of the work quoted in connection with contemporary knowledge. The selections chosen are grouped in eight main divisions or chapters, corresponding to the usual divisions of didactic Physiology. Within each group the arrangement is chronological. The choice of the individual readings might well be a subject for discussion among physiologists and medical historians, less in respect to the investigators included as to whether the paragraphs selected are the most important or the most significant among their writings. Individual viewpoint will reflect that of the editor. To the student of the history of physiology this book is a most excellent introduction.

matter and in literary value. Interest is well sustained throughout. The illustrations are not the familiar ones from medical histories, and the liberal use of reproductions of title pages will appeal to the book lover. This book should be read by every medical student as collateral reading in the second half of his course in physiology. Many practitioners will appreciate it and it should be a popular gift book among a large group interested in the biological sciences.

Protozoan Parasitism of the Alimentary Tract: Pathology, Diagnosis, and Treatment. By KENNETH M. LYNCH, M.D., Professor of Pathology, Medical College of the State of South Carolina, Charleston, South Carolina. xviii + 258 pages, 37 illustrations. The MacMillan Company, New York City, 1930. Price, \$3.75.

To serve as a connecting link between systematic protozoology and clinical medicine in respect to the protozoan parasites of the alimentary tract is the purpose of this monograph. The author properly recognizes that most practitioners of medicine are concerned only with the pathogenic significance, recognition and treatment of a limited number of important parasites. Technical descriptions, such as the professional protozoologist would require, are largely omitted or rewritten in a manner understandable to those doing medical laboratory work. Procedures are outlined for routine stool examinations. Especially to be commended are the strongly put warnings against assigning unwarranted importance to fairly constant protozoan inhabitants of the intestinal tract when scientific evidence of pathogenic significance is lacking. More carefully systematized descriptions of gross and microscopical pathology would be useful. The claims of Kofoid and his associates in respect to finding *Endamoeba histolytica* in the tissues of joints in

arthritis deformans and in the lymph nodes in Hodgkin's disease are properly discredited. Treatment is fully outlined in respect to those organisms known to be pathogenic. This book will correct many false impressions which are commonly held.

Discovering Ourselves, A View of the Human Mind and How it Works. By EDWARD A. STRECKER, A.M., M.D., Professor of Nervous and Mental Diseases, Jefferson Medical College, Philadelphia, and KENNETH E. APPEL, Ph.D., M.D., Assistant Professor of Psychiatry, School of Medicine, University of Pennsylvania. xiii + 306 pages, 28 illustrations. The MacMillan Company, New York City, 1931. Price, \$3.00.

This is a book for the individual, about himself, and it is a book with a mission. Although it deals with the fundamentals of normal and abnormal psychology, it is never abstruse, or unclear, or dull. It can be read by every medical man and every intelligent layman, too, with pleasure and profit. It succeeds in avoiding the specialized terminology of psychology, substituting well understood and yet scientifically accurate expressions for the vernacular of the specialist. The authors thus state their objective: "If the stakes in the game of physical hygiene are health and life, then the stakes in the game of mental hygiene are even higher, efficiency or inefficiency, success or failure, happiness or unhappiness, replete, satisfying, and worth while lives or empty, unsatisfactory, and pathetic existences, sanity or insanity. It is to the realization of the constructive potentialities of the human mind that this book is dedicated." The physician who has a sympathetic grasp of its content will find that he can prescribe this book with profit to certain of his patients.

College News Notes

The American College of Physicians began to publish an official journal, known as "Annals of Clinical Medicine", July, 1922. It is interesting to note that the following members contributed to that number.

Dr James M Anders, (Master)

Dr. Sydney R Miller, (Fellow)

Dr Leonard M Murray, (Fellow)

Dr C C. Bass, (Fellow)

Dr Louis M Gompertz (Deceased),
(Associate)

Dr. William Carpenter MacCarty, (Fellow)

Dr Leo L. Hardt, (Fellow)

Dr. Vernon C Rowland (Fellow), Cleveland, was the official representative of the American College of Physicians, appointed by the President, on the occasion of the formal dedication of the Lakeside Hospital group at Cleveland, June 7, when Western Reserve University brought to completion its \$15,000,000 Medical Center. From all sections of the country delegates of the leading scientific, medical, educational, social and civic organizations came to attend the ceremonies and pay tribute to this institution. The address of dedication was delivered by Dr. Hans Zinsser, Professor of Bacteriology of Harvard University Medical School. Later, Western Reserve University conferred upon Dr. Zinsser the honor degree of Doctor of Science. Thus decorated was also conferred upon Dr. David H. W. H. H. H., Director of Laboratories, Massachusetts General Hospital, and Assistant Professor of Pathology at Columbia University; Dr. J. P. H. H. H., Surgeon, Dr. J. H. H. H., Professor of Surgery, Dr. J. H. H. H., Professor of Medicine, Dr. J. H. H. H., Professor of Surgery, Dr. J. H. H. H., Professor of Medicine, Dr. J. H. H. H., Professor of Surgery, Dr. J. H. H. H., Professor of Medicine.

Newton Richards, Professor of Pharmacology at the University of Pennsylvania School of Medicine The degree of Doctor of Laws was conferred upon Dr. Henry A. Christian (Fellow), Hersey Professor of the Theory and Practice of Physic at Harvard University Medical School, and on Dr. James Ewing, Professor of Pathology, Cornell University Medical College

Dr William Gerry Morgan (Fellow), Washington, D C, was recently elected a member of the Board of Regents of Georgetown University

Dr E J G Beardsley (Fellow), Philadelphia, gave the graduation address of the Medical Field Service School at Carlisle Barracks, Carlisle, Pa, May 30, 1931, upon "Service Ideals, the Medical Profession and the Public".

On June 17, 1931, Dr. Beardsley addressed the members of the Hazleton (Pa.) Medical Society upon "Medical Art in Connection with Cardiovascular Disorders".

Dr Frank B. Cross (Fellow), Brooklyn, on May 19, addressed the Medical Society of the County of Kings on "Stimulation of the Renal Secretion".

"What the Doctor of Internal Medicine Expects from the Occupational Therapist" was the subject of an address delivered by Dr. Walter P. Anderson (Fellow), New York, N. Y., May 22, before the Brooklyn Society of Internal Medicine.

Dr. Henry M. Moses (Fellow) Brooklyn, N. Y., read a paper on "Carcinoma of the Lung," May 12, at the meeting of the Medical Society of Bay Ridge.

Dr. William J. Keer (Fellow), San Francisco, is listed as one of the presenters.

ers at the annual meeting of the Canadian Medical Association, June 22-26 Dr Kerr's subject was "Coronary Occlusion"

Dr Israel M Rabinowitch (Fellow), Montreal, addressed the same meeting on "Diabetes"

Dr Anton J Carlson (Fellow), Chicago, and Dr Fred Moore (Fellow), Des Moines, are members of the Committee appointed to follow up the findings of the medical service section of the White House Conference on Child Health and Protection, as announced by Secretary Ray Lyman Wilbur on May 20 Dr Wilbur is Honorary Chairman of this Committee The findings of this Committee will be distributed to those organizations that are striving to improve the health of children

Dr Thomas B Fitcher (Fellow), Baltimore, and Dr James H Means (Fellow), Boston, were elected President and Secretary, respectively, of the Association of American Physicians at its annual meeting on May 6

Dr Cyrus C Sturgis (Fellow), Ann Arbor, was elected Secretary of the American Society for Clinical Investigation on May 4

The following Fellows of the College addressed the American Heart Association on June 9, during its seventh annual meeting, in Philadelphia

Dr Fred M Smith, Iowa City
Dr Stewart R Roberts, Atlanta
Dr John H Musser, New Orleans
Dr David Riesman, Philadelphia
Dr James B Herrick, Chicago
Dr Paul D White, Boston
Dr Emanuel Libman, New York

Dr Elliott P Joslin (Fellow), Boston, recently addressed the George Washington University Medical School on diabetes

Dr William Engelbach (Fellow), New York, on June 20 addressed the Schuyler County (Ill) Medical Society on "Diagnosis and Treatment of Endocrine Disorder".

Dr Fred M Smith (Fellow), Iowa City, delivered an address on "Arteriosclerotic Heart Disease", April 9, before the Linn County (Iowa) Medical Society

Dr Jeannette Dean Throckmorton (Fellow), Des Moines, was recently elected Treasurer of the Iowa State Medical Women Society

Dr George R Minot (Fellow), Boston, presented a paper on "Adequate Treatment of Anemia" before the Plymouth District Medical Society on May 21 at Abington

Dr Paul D White (Fellow), Boston, spoke on "Precordial Pain and Tenderness" at a meeting of the cardiac course of the New England Heart Association on May 13

Dr Frank Vander Bogert (Fellow), Schenectady, used as his subject "Feeding of Sick Children" in an address, May 12, before the Medical Society of the County of Washington (New York)

Dr Lawrason Brown (Fellow), Saranac Lake, and Dr James B Herrick (Fellow), Chicago, are on the tentative program of the Oklahoma City Clinical Society, which will hold its annual fall conference November 2-5

The following Fellows of the College addressed the Garfield County (Okla) Medical Society, April 9, as indicated

Dr Porter P Vinson—"Diagnosis and Treatment of Cardiospasm",

Dr John H Musser—"Acute Infections",
Dr Charles A Elliott—"Blood Pressure"

Dr Donald R Ferguson (Fellow), Philadelphia, Clinical Professor of Medicine at the Hahnemann Medical College, was recently elected President of the Philadelphia County Homeopathic Medical Society

Dr Franklin F Murdoch (Fellow), Lieutenant Commander, U S Navy, was appointed during June, Professor of Tropical Medicine at the George Washington University Medical School

College News Notes

The American College of Physicians began to publish an official journal, known as "Annals of Clinical Medicine", July, 1922. It is interesting to note that the following members contributed to that number

Dr James M Anders, (Master)

Dr Sydney R Miller, (Fellow)

Dr Leonard M Murray, (Fellow)

Dr C C Bass, (Fellow)

Dr Louis M Gompertz (Deceased), (Associate)

Dr. William Carpenter MacCarty, (Fellow)

Dr Leo L Hardt, (Fellow)

Dr Vernon C Rowland (Fellow), Cleveland, was the official representative of the American College of Physicians, appointed by the President, on the occasion of the formal dedication of the Lakeside Hospital group at Cleveland, June 7, when Western Reserve University brought to completion its \$15,000,000 Medical Center. From all sections of the country delegates of the leading scientific, medical, educational, social and civic organizations came to attend the ceremonies and pay tribute to this institution. The address of dedication was delivered by Dr. Hans Zinsser, Professor of Bacteriology of Harvard University Medical School. Later, Western Reserve University conferred upon Dr Zinsser the honorary degree of Doctor of Science. This degree was also conferred upon Dr David Marine (Fellow), Director of Laboratories, Montefiore Hospital, and Assistant Professor of Pathology at Columbia University College of Physicians and Surgeons, Dr Samuel C Harvey, Professor of Surgery, Yale University School of Medicine, Dr. Hart A Graham, Professor of Surgery, Washington University School of Medicine, Dr Alphonse R Dochez, Professor of Medicine, Columbia University College of Physicians and Surgeons, and Dr Alfred

Newton Richards, Professor of Pharmacology at the University of Pennsylvania School of Medicine. The degree of Doctor of Laws was conferred upon Dr Henry A Christian (Fellow), Hersey Professor of the Theory and Practice of Physic at Harvard University Medical School, and on Dr James Ewing, Professor of Pathology, Cornell University Medical College

Dr. William Gerry Morgan (Fellow), Washington, D C, was recently elected a member of the Board of Regents of Georgetown University

Dr E J G Beardsley (Fellow), Philadelphia, gave the graduation address of the Medical Field Service School at Carlisle Barracks, Carlisle, Pa, May 30, 1931, upon "Service Ideals, the Medical Profession and the Public"

On June 17, 1931, Dr. Beardsley addressed the members of the Hazleton (Pa) Medical Society upon "Medical Art in Connection with Cardiovascular Disorders"

Dr Frank B Cross (Fellow), Brooklyn, on May 19, addressed the Medical Society of the County of Kings on "Stimulation of the Renal Secretion"

"What the Doctor of Internal Medicine Expects from the Occupational Therapists" was the subject of an address delivered by Dr Walter P Anderton (Fellow), New York, N Y, May 22, before the Brooklyn Society of Internal Medicine.

Dr Henry M Moses (Fellow) Brooklyn, N Y, read a paper on "Carcinoma of the Lung", May 12, at the meeting of the Medical Society of Bay Ridge

Dr. William J Kerr (Fellow), San Francisco, was included among the guest speak-

ers at the annual meeting of the Canadian Medical Association, June 22-26 Dr Kerr's subject was "Coronary Occlusion"

Dr Israel M Rabinowitch (Fellow), Montreal, addressed the same meeting on "Diabetes"

Dr Anton J Carlson (Fellow), Chicago, and Dr Fred Moore (Fellow), Des Moines, are members of the Committee appointed to follow up the findings of the medical service section of the White House Conference on Child Health and Protection, as announced by Secretary Ray Lyman Wilbur on May 20 Dr Wilbur is Honorary Chairman of this Committee The findings of this Committee will be distributed to those organizations that are striving to improve the health of children

Dr Thomas B Futeher (Fellow), Baltimore, and Dr James H Means (Fellow), Boston, were elected President and Secretary, respectively, of the Association of American Physicians at its annual meeting on May 6

Dr Cyrus C Sturgis (Fellow), Ann Arbor, was elected Secretary of the American Society for Clinical Investigation on May 4

The following Fellows of the College addressed the American Heart Association on June 9, during its seventh annual meeting, in Philadelphia

Dr Fred M Smith, Iowa City
Dr Stewart R Roberts, Atlanta
Dr John H Musser, New Orleans
Dr David Riesman, Philadelphia
Dr James B Herriek, Chicago
Dr Paul D White, Boston
Dr Emanuel Libman, New York

Dr Elliott P Joslin (Fellow), Boston, recently addressed the George Washington University Medical School on diabetes

Dr William Engelbach (Fellow), New York, on June 20 addressed the Schuyler County (Ill) Medical Society on "Diagnosis and Treatment of Endocrine Disorder".

Dr Fred M Smith (Fellow), Iowa City delivered an address on "Arteriosclerotic Heart Disease", April 9, before the Linn County (Iowa) Medical Society

Dr Jeannette Dean Throckmorton (Fellow), Des Moines, was recently elected Treasurer of the Iowa State Medical Women Society

Dr George R Minot (Fellow), Boston, presented a paper on "Adequate Treatment of Anemia" before the Plymouth District Medical Society on May 21 at Abington

Dr Paul D White (Fellow), Boston, spoke on "Precordial Pain and Tenderness" at a meeting of the cardiac course of the New England Heart Association on May 13

Dr Frank Vander Bogert (Fellow), Schenectady, used as his subject "Feeding of Sick Children" in an address, May 12, before the Medical Society of the County of Washington (New York)

Dr Lawrason Brown (Fellow), Saranac Lake, and Dr James B Herriek (Fellow), Chicago, are on the tentative program of the Oklahoma City Clinical Society, which will hold its annual fall conference November 2-5

The following Fellows of the College addressed the Garfield County (Ola) Medical Society, April 9 as indicated

Dr Porter P. Vinson—"Diagnosis and Treatment of Cardiospasm"

Dr John H Musser—"Acute Infections";

Dr Charles A Elliott—"Blood Pressure"

Dr Donald R Ferguson (Fellow), Philadelphia, Clinical Professor of Medicine at the Hahnemann Medical College was recently elected President of the Philadelphia County Homeopathic Medical Society

Dr Franklin P. Woodbury (Fellow), Lieberman, Commander, U. S. Navy, was appointed director of Tropical Medicine at the George Washington University Medical School

Dr. James Craig Small (Fellow), Philadelphia, was elected an honorary member of Phi Beta Kappa, Iota Chapter of Pennsylvania, on June 6, 1931, the twentieth anniversary of his graduation from Gettysburg College

Dr M Murray Peshkin (Fellow), New York, delivered a paper on "A Dry Pollen Ophthalmic Test in Asthma and Hay Fever Patients Negative to Cutaneous Tests", June 9, before the American Association for the Study of Allergy at Philadelphia. The technic of the dry pollen eye test and the various positive reactions in natural colors were shown in the Allergy Section of the Scientific Exhibit of the American Medical Association during the week of June 8

Dr Michael Vinciguerra (Fellow), Elizabeth, N J, was recently appointed Assistant in Neurology at Columbia University and Assistant Visiting Physician in Neurology at Columbus Hospital.

Dr Mortimer Warren (Fellow), Portland, Maine, was awarded the degree of Doctor of Science by Bowdoin College on June 18, 1931

Dr Fred M Smith (Fellow), Iowa City, was elected President of the Iowa Heart Association on May 15

Dr Alexander G Brown, Jr (Fellow), Richmond, Va, participated in the unveiling of a tablet to the honor of Dr William Brown, his great-great-great-grandfather who was the Surgeon General of the Continental Army during the American Revolution. The unveiling exercises took place June 14 at 212 S Fairfax Street, Alexandria, Va, the bronze tablet being placed on the old home of Dr Brown

Dr John A Macgregor (Fellow), London, Ont, was the recipient of the degree of Doctor of Laws, conferred by the Senate of the University of Western Ontario at the June Convocation. Dr Macgregor is Professor Emeritus of Medicine of the University of Western Ontario Faculty of Medicine.

Dr Ross V Patterson (Fellow), Philadelphia, Dean of Jefferson Medical College and President of the Medical Society of the State of Pennsylvania, received the degree of Doctor of Science from La Salle College on May 24

Dr Horton R Casparis (Fellow), Nashville, delivered an address on "Tuberculosis in Children" on May 28 at the first of four joint meetings to be held by the Medical Societies of Roane, Monroe, Loudon and McMinn Counties (Tenn).

At the recent annual meeting of the West Virginia State Medical Association, Dr Albert H Hoge (Fellow), Bluefield, was elected President. Dr Hoge will assume office on January 1, 1932

Dr Walter Simpson (Fellow), Dayton, and Dr Cyrus C Sturgis (Fellow), Ann Arbor, addressed the Pacific Northwest Medical Association, June 25-27, at Seattle on "Tularemia" and "Treatment of Pernicious Anemia", respectively

At the annual meeting of the American Climatological and Clinical Association, on May 8, Dr Louis Hamman (Fellow), Baltimore, was elected President

During the recent meeting in Philadelphia of the Association for the Study of Allergy, Dr Albert H W Caulfeild (Fellow), Toronto, was elected President-Elect, and Dr Warren T. Vaughan (Fellow), Richmond, was elected Secretary-Treasurer

Dr Lyell C Kinney (Fellow), San Diego, participated in a symposium on medical economic problems, which was presented before the San Diego County Medical Society on June 9

Dr Oscar M Gilbert (Fellow), Boulder, Colo, addressed the Boulder County Medical Society, June 11, on "Coronary Sclerosis in Diabetes"

Dr Lester R Dragstedt (Fellow), Chicago, gave an illustrated lecture on "Acute

Intestinal Obstruction" before the Twelfth District Medical Society, May 26, at Fort Wayne, Indiana

Dr Frederick G Banting (Fellow), Toronto, Ont, spoke before the students and faculty of the University of Michigan Medical School, May 8, on "The History of Insulin"

At the clinic of the Kansas City Southwest Clinical Society, June 9, Dr Peter T Bohan (Fellow), Kansas City, spoke on "Intercostal Neuralgia Simulating Visceral Disease"

Dr Henry Kennon Dunham (Fellow), Cincinnati, was re-elected President of the Ohio Public Health Association on June 4

Dr John H Peck (Fellow), Des Moines, was elected one of the Vice Presidents of the National Tuberculosis Association at its meeting in Syracuse on May 11-14

Dr James B Herrick (Fellow), Chicago, member of the Class of 1888, Rush Medical College, acted as Toastmaster at the annual dinner of the faculty and alumni during the Rush Homecoming Week

Lieutenant Colonel W Lee Hart (Fellow), has been transferred from the Army War College to Omaha, seventh corps area

Captain John D Brumbaugh (Associate), has retired from the Medical Corps of the U S Army due to incapacitation from active service

Lieutenant Colonel William L Sheep (Fellow), has been assigned to Balboa Heights, Canal Zone, as has also Lieutenant Colonel Ernest R Gentry (Fellow).

The following Fellows of the College held a Clinic for the physicians of South Carolina at the South Carolina State Sanatorium, Columbia, July 29-30

Dr R P McCam, Sanatorium, N C
Dr Paul Ringer, Asheville, N. C
Dr J B Sidbury, Wilmington, N C

Dr Thomas Addis (Fellow), Stanford University Medical School, San Francisco, has been selected to deliver the William Sydney Thayer lecture at Johns Hopkins University School of Medicine this year

At the Texas State Medical Society's meeting in May, the following Fellows were among the out-of-state speakers

Dr Clifford A Barborka, Rochester, Minn

Dr William C MacCarty, Rochester, Minn

Dr Tom B Throckmorton, Des Moines, Iowa

Dr Ralph Pemberton (Fellow), Philadelphia, is a charter member of the newly organized American Society of Physical Medicine. The aims of this organization are to improve the practice of physical medicine, promote research, encourage clinical investigation and advance the teaching of physical medicine. The Officers are

Dr John S Coulter, Chicago, President,
Dr K G Hansson, New York, Vice President,

Dr Willis S Peck, Ann Arbor, Secretary and Treasurer

Dr George Herrmann (Fellow), formerly Associate Professor of Medicine at Tulane University of Louisiana School of Medicine, will go to the University of Texas as Professor of Clinical Medicine at the opening of the fall term. His new address is The John Sealy Hospital 810 Avenue B, Galveston Texas

Dr John E Waller (Fellow), Opelika, Ala, is the author of an article on "The Germicidal and Therapeutic Applications of Soaps", which appeared in the Journal of the American Medical Association July 2, 1931

Dr Waller addressed the Central Valley Medical and Surgical Association at Albany, Cal, July 15, 1931. The Club Recognition of the Central Valley Medical and Surgical Association

Dr A G Schwach (Fellow), Honolulu, Hawaii, and Dr K S Dancy (Fellow), Los Angeles, Calif, are authors of "Clinical

Appendicitis" and "Atypical Bone Tumors with Presentation of Two Cases", respectively, appearing in the July issue of Radiology

Dr William Egbert Robertson (Fellow), Philadelphia, was one of the speakers at the dedication of the Quakertown Community Hospital, Quakertown, Pa, on June 21. The hospital was erected at a cost of \$200,000, raised by public subscription

Dr Elmer Funk (Fellow), Philadelphia, was Toastmaster at the Alumni Dinner of Jefferson Medical College, July 3, when a large number of the Alumni celebrated the 160th annual Ex-Interns' Day and Alumni Day. Dr Ross V Patterson (Fellow), was one of the speakers, and, as Dean of Jefferson Medical College, accepted an oil portrait of Dr John M Fisher, Associate Professor of Gynecology, the oldest ex-intern of Jefferson Hospital

Among Fellows of the College who have recently been appointed to the Abington (Pa.) Memorial Hospital are the following

Dr Henry L Bockus, Professor of Gastro-enterology of the University of Pennsylvania Graduate School of Medicine,

Dr John Eiman, Assistant Professor of Pathology, University of Pennsylvania Graduate School of Medicine,

Dr George Morris Piersol, Professor of Medicine, University of Pennsylvania Graduate School of Medicine,

Dr G Harlan Wells, Professor of Medicine, Hahnemann Medical College,

Dr William D Stroud, Associate Professor, Diseases of the Heart, University of Pennsylvania Graduate School of Medicine,

Dr. Harry B Wilmer, Associate Professor of Medicine, University of Pennsylvania Graduate School of Medicine

Dr Arthur W White (Fellow), Oklahoma City, Okla, is author of an article entitled "Clinical Aspects of Gastric and Duodenal Ulcer" in the July issue of the Journal of the Oklahoma State Medical Association

Doctors Claiborne T Smith (Fellow), and William Bernard Kinlaw (Fellow), both of Rocky Mount, N C, were the recipients of the Moore County (N C) Medical Society's medal for having presented the best paper at the 1930 meeting of the North Carolina State Medical Society, the medal being presented during the last annual meeting of the State Society at Durham

Dr Charles G Jennings (Fellow), Detroit, was elected Honorary President of the Medical Alumni Association of the Detroit College of Medicine and Surgery on June 18, the occasion of its 61st Reunion. Dr Jennings is the oldest graduate of the College, having been graduated in 1879

Dr Ernest H Falconer (Fellow) and Dr Hans Lisser (Fellow), both of San Francisco, were recently advanced from Associate Clinical Professors of Medicine to Clinical Professors of Medicine in the University of California Medical School

Dr Thomas B Futcher (Fellow) and Dr Louis Hamman (Fellow), both of Baltimore, were among the invited speakers before the Mahoning County Medical Society at Youngstown on June 18, the occasion of its 5th annual postgraduate day. Dr. Futcher delivered two addresses, one on "The Problem of Arthritis in General Practice" and the other, "Manifestations of Hyperfunction and Hypofunction of the Endocrine Glands". Dr Hamman also delivered two addresses, one on "Diagnosis of Obscure Fevers", and the other, "Diagnosis of Coronary Occlusion"

Dr Willard C Rappleye (Fellow), Dr Walter W Palmer (Fellow), and Dr Arthur F. Chace (Fellow), all of New York City, have been appointed by President Nicholas Murray Butler, of Columbia University, members of the Administrative Board of Postgraduate Studies in Medicine, to have general control of all postgraduate instruction in medicine under the auspices of the University. The New York Postgraduate Medical School and Hospital became on July 1, the Postgraduate School of Medicine of Columbia University.

Dr Waller S Leathers (Fellow), Nashville, addressed the Christian County Medical Society at Hopkinsville, Ky, June 16, on "Significant Achievements in the Field of Preventive Medicine"

Dr Leathers is Dean and Professor of Preventive Medicine and Public Health at Vanderbilt University School of Medicine. He was recently re-elected President of the National Board of Medical Examiners

Dr. Charles E. Homan, Jr (Fellow), Chattanooga, addressed the Chattanooga and Hamilton County Medical Society, June 4, on "Spastic Colon"

Dr Karl H. Doege (Associate), Marshfield, Wis, addressed the Wood County (Wis) Medical Society, June 25, on "Some Aspects of Acute Rheumatic Fever"

Dr Hyman I. Goldstein (Associate), Camden, N. J., read a paper before the American Therapeutic Society, held at Atlantic City during June, on "Streptococcal Fautitis with Erythema Nodosum and Erythema Multiforme Exudativum Diagnosis and Treatment"

Dr H. Sheridan Baketel (Fellow), Jersey City, spoke on "Present Trends in the Practice of Medicine" at a meeting of the Fifth Councilor District of the Medical Society of New Jersey, at Atlantic City, April 10th. On June 24th he spoke to the physicians of the Lehigh Valley at Bethlehem, Pa, on the "Economics of Medical Practice"

Dr Jacob M. Cahan (Fellow), Philadelphia, addressed the local Medical Inspectors of Public Schools on the subject of Heart Disease in Children, presenting cases with various lesions, on June 30th, 1931

The American Congress of Physical Therapy

The tenth anniversary session of the American Congress of Physical Therapy will be held October 5, 6, 7, and 8, 1931, at the Hotel Fontenelle, Omaha, Nebraska. A preliminary program and other information can be obtained from the American Congress of Physical Therapy, 30 North Michigan Avenue, Chicago, Ill

Acknowledgment is made of the following gifts of reprints by members of the College to the College Library:

Dr Clarence H. Boswell (Fellow), Rockford, Ill.—1 reprint

Dr Arthur C. Clasen (Fellow), Kansas City, Mo.—4 reprints

Dr M. J. Fein (Associate), Brooklyn, N. Y.—1 reprint

Dr Hyman I. Goldstein (Associate), Camden, N. J.—1 reprint

Dr John F. W. Mcagher (Fellow), Brooklyn, N. Y.—16 reprints

Dr Roy D. Metz (Fellow), Detroit, Mich.—1 reprint

Dr Karl Rothschild (Associate), New Brunswick, N. J.—2 reprints

Dr Carl V. Vischer (Fellow), Philadelphia, Pa.—1 reprint

Dr George L. Waldbott (Fellow), Detroit, Mich.—2 reprints

OBITUARIES

*DOCTOR REYNOLD WEBB
WILCOX*

Dr. Reynold Webb Wilcox (Fellow), first President and charter member of the American College of Physicians, died at his home in Princeton, N. J., June 6, 1931; aged, 75 years

Dr. Wilcox was born in Madison, Conn. He attended the Lee's Academy for his elementary education, and graduated from Yale University with the degree of Bachelor of Arts in 1878. He received his medical training at Harvard University Medical School, graduating in 1881. He held the honorary degrees of Master of Arts from Hobart College in 1881; Doctor of Laws from Maryville College in 1892; and Doctor of Civil Law from Wittenberg College in 1915. He did post-graduate work at the New York Post-graduate Medical School and Hospital, in which institution he later became Professor of Medicine. He was formerly on the Staffs of St. Mary's Hospital (New York), Ossining Hospital (New York), Eastern Long Island Hospital (Greenport, N. Y.), Nassau Hospital (Mineola) and the New Jersey State Hospital (Greystone Park). He was the author of more than three hundred and fifty articles published in various American journals. He was also author of "Materia Medica and Therapeutics", of which ten editions were published, also "Treatment of Disease", five editions; and several other books.

He was a member of the Revision Committee of the U. S. Pharmacopoeia in 1900-1910.

His memberships in scientific societies included the Harvard Medical Society, Medical Association of Greater New York, American Academy of Medicine, American Association of Military Surgeons, Society of Medical Jurisprudence, American Association on Medical Jurisprudence, American Association for Advancement of Science, American Therapeutic Society, Connecticut State Medical Association, American Medical Association, American Congress on Internal Medicine, and others.

Dr. Wilcox, with a small group of Internists, conceived the idea of the organization of the American College of Physicians, for which they secured a charter on May 11, 1915, under the laws of the State of Delaware. He became the first President, continuing in office until 1922. In recent years, he had been more or less incapacitated in health, but maintained an active and personal interest in the activities and work of the College.

*DOCTOR ARTHUR CLIFFORD
SELMON*

Dr. Arthur Clifford Selmon (Fellow), Battle Creek, Mich., died suddenly, May 16, of chronic myocarditis; aged, 53 years.

Dr. Selmon was born near Columbus Junction, Iowa, in 1877. He attended the Iowa State Normal School, then entered the Keokuk Medical College from which he later transferred to the American Medical Missionary College, receiving the degree of Doctor of Medicine in 1902. In 1903, he began missionary work in China. Honan

Province, where he remained for ten years. For eleven additional years he was engaged in missionary work in Shanghai as Internist to the Shanghai Sanitarium. During this time, he, with the help of Chinese scholars, edited a book on "Health and Longevity", written in Chinese. This book is a contribution to the cause of disease prevention in that country where, lacking health departments, the individual was the only approach to the problem. About fifty thousand copies of this book in Chinese have been distributed. It has been translated into fifteen other languages and a translation into Arabic is contemplated.

He pursued postgraduate study in Hematology at Tulane University of Louisiana School of Medicine, and in Blood Chemistry, Physical Diagnosis and Internal Medicine at the New York Postgraduate Medical School. In 1925, he became Staff Physician of the Kellogg Company, Battle Creek, which position he held until the recent creation of the W. K. Kellogg Foundation. During the five years that Dr. Selmon was in charge of the Kellogg Company Hospital, the average lost time because of sickness or injury on the part of Kellogg employees was reduced to such a degree as to establish a record for industries of the United States. Many departments were added to the hospital under Dr. Selmon's direction, until it is now one of the model industrial hospitals of the world.

As Associate Medical Director of the W. K. Kellogg Foundation, Dr. Selmon was enthusiastically and energetically organizing the plans of carrying out the purposes of the

Foundation, including the studying of the childhood causes which are blighting influences in life later on, as perhaps in his own case, an early typhoid fever may have been a factor in his untimely death.

(Furnished by Stuart Pritchard, M.D., F.A.C.P., Battle Creek, Mich.)

DOCTOR HORACE HOWARD JENKS

Dr. Horace Howard Jenks (Fellow), Philadelphia, died July 6, 1931, of bronchopneumonia, aged fifty-three years.

Dr. Jenks was born at Ashbourne, Montgomery County, Pa., June 7, 1878. He attended Haverford College, from which he graduated with the degree of Bachelor of Arts in 1900 whereupon he entered the University of Pennsylvania School of Medicine from which he graduated in 1904 with the degree of M.D. Dr. Jenks was Associate in Pediatrics, University of Pennsylvania School of Medicine from 1927 to 1929, and Assistant Professor of Pediatrics in the University of Pennsylvania Graduate School of Medicine from 1926 to date of his death. He was Assistant Visiting Physician, 1924 to 1930, and Visiting Physician, 1930 to the time of his death, to the Children's Hospital, Visiting Physician to St. Christopher's Hospital for Children since 1927 and Medical Director of the Associated Medical Clinics since 1920.

Dr. Jenks was a Fellow of the Philadelphia College of Physicians and of the American Medical Association. He was elected a Fellow of the American College of Physicians on November 11, 1930. Other memberships included the Philadelphia Pediat-

nic Society, the Philadelphia County Medical Society, the Pennsylvania State Medical Association and the American Pediatric Society. Dr. Jenks was honored by election to office in several of these organizations. He had served as President of the Philadelphia Pediatric Society, and at the time of his death was Chairman of the Certified Milk Commission of the Philadelphia Pediatric Society. To this latter position, he brought his wealth of experience and ability as an executive and organizer which he had demonstrated so thoroughly in his connection with the Associated Medical Clinics organized and developed to a high degree of efficiency by him. Quiet in dignity and reserved in manner, Dr. Jenks had a host of friends not only among his patients but also among his colleagues and associates. In his sudden death the medical profession has lost an earnest and conscientious member, the community, a citizen of greatest worth, and his family, a husband and father whose love will be cherished forever.

Furnished by Miss E. Siegel, M.D. (F.A.C.P., Philadelphia, Pa.)

DOCTOR HARRY M. HALL

Dr. Harry M. Hall (Fellow), Wheeling, W. Va., died, June 6, 1931, aged, 53 years.

Dr. Hall was born in Wheeling and received his elementary training in the Wheeling Public Schools. He attended Western Reserve University of Medicine, from which he received the Degree of Doctor of Medicine in 1898. For many years, he was a member of the Staff and Instructor of Nurses in Principles of Medicine of the Ohio Valley General Hospital. At the time of his death, he was Director of the West Virginia Tuberculosis and Health Association and Associate Editor of the West Virginia Medical Journal. He was Councilor-at-large of the West Virginia State Medical Association, having been President of that organization in 1929-1930. He became a Fellow of the American College of Physicians on November 17, 1928. He was also a member of the Ohio County Medical Society, and a Fellow of the American Medical Association.

Observations on Rheumatic Pancarditis and Infective Endocarditis*

By W S THAYER, M D , F A C P , *Baltimore, Md*

WE now know that the endocarditis of rheumatism on which so much stress has been laid in the past is but one of the manifestations of a general process, the most important feature of which, though often not the most prominent, is the cardiac disease. This cardiac disease is a general involvement of the heart in which valvular affections, acute, subacute and chronic, often, but by no means always, play a relatively important part. Indeed in the more acute and not infrequently in the more chronic forms of the malady the changes in the muscle or in the pericardium are of graver import than the sometimes more obvious endocarditis. There are other manifestations of rheumatic fever beside those in the joints and in the heart, notably changes in vessels, skin and nervous system which are rather characteristic.

That the rheumatic process is infectious is reasonably clear. That this infection is related to certain forms of streptococci is not improbable but cannot be said to have been proven. The nesting of bacteria at the seats of the characteristic focal lesions has not been demonstrated, and the inviting hypotheses of Weintiaud, Benzançon, Swift, Coburn and others who believe that the lesions and symptoms of the rheumatic disease may be dependent

upon an allergic process like that observed in syphilis or tuberculosis are not universally accepted.

Doubtless of infectious origin rheumatic heart disease may yet be distinguished from that which we call "bacterial" or "infective" endocarditis. Here the endocarditis, focal lesions on valves, mural endocardium or the intima of a larger vessel, is the essential seat of the disease the spot at which is kept alive the infection to which, more or less directly, death is usually due.

The following observations are based largely on a study of sixty-five cases of rheumatic endocarditis with necropsy, fatal during a period of activity of the rheumatic process along with a series of three hundred and six cases of infective endocarditis of which two hundred and six came to necropsy†.

*Presented at the Baltimore meeting of the American College of Physicians March 23 1931.

†The Gibson Lectures Edmh Med Jr 1931, n s, LXXXIII, 237-265, 307-334. In this article numerous references to the literature may be found which have not been included in this communication. For further references the reader is referred to the admirable monograph of Lemerre and Deschamps *Les endocardites infectieuses diagnostic et traitement* 1930 S G Denot et Cie, 1930.

It is possible to distinguish roughly two forms of rheumatic heart disease (1) The acute malignant pancarditis occurring usually in youth with high fever, pronounced leucocytosis and general appearances which might easily be associated with an acute bacterial endocarditis. In such cases death may result within a few weeks, or, gradually, the process may become subacute and end in recovery with surprising improvement in the apparent cardiac impairment but with a resultant chronic valvular disease. Sometimes the fever pursues so regular an intermittent course and lasts so long that the picture may resemble a subacute or chronic vegetative endocarditis. (2) The more subacute and chronic forms of the disease. Here, while the onset is usually characteristic of an acute rheumatic fever, yet sometimes the arthritis, the fever, the signs of cardiac involvement may for long periods be so slight and indefinite that disease of the heart may be un-

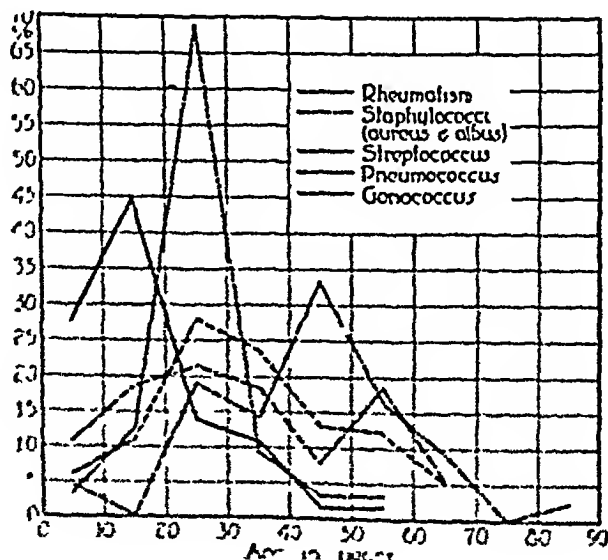
suspected. This is especially true in early childhood.

There are certain rather distinctive features of rheumatic heart disease.

Rheumatic carditis is essentially a disease of youth and adolescence.

Nearly three-quarters of our fatal instances of rheumatic endocarditis with necropsy died in the first and second decades. How striking this phenomenon is is emphasized in Chart 1. In no other form of cardiac disease is the fatal issue so common in the early decades of life. Indeed in a hospital where for years, there was no large children's ward, nearly 28 per cent of patients showing acute rheumatic endocarditis at necropsy, were under the age of 10, over 72 per cent under 20. One has but to glance at the chart to see how different are the figures in infective endocarditis.

Rheumatic heart disease is essentially subacute leading to chronic valvular disease. Nearly two-thirds of these patients dying with evidences of



acute rheumatic cardiac disease showed clinical or post-mortem evidence of pre-existing chronic valvular changes. Not infrequently where the fatal attack was supposed to be primary, clinical and pathological evidence of previous changes were found indicating what should be more generally realized, namely that the early rheumatic cardiac changes may steal on the patients like a thief in the night. Often, as Swift especially has pointed out, the fever is moderate or even absent for considerable periods of time and arthritis is trivial or absent. There were long remissions and frequent recurrences. Chills are rare. Embolic phenomena were never observed except in instances of marked myocardial insufficiency, usually in association with auricular fibrillation.

Petechiae are rare in rheumatic endocarditis. In not one of our sixty-five fatal cases were petechiae observed. Anemia as a rule was rather moderate although there was a fairly

well marked leucocytosis averaging between 14,000 and 18,000 per cu mm, very much like that in subacute infective endocarditis, (Chart 2). Albuminuria was common at the height of the disease but acute glomerulonephritis, so frequent in infective endocarditis, was not observed. Acute suppurative processes common in some infective endocarditides, were not seen.

Serofibinous pericarditis is a common and characteristic manifestation of rheumatic cardiac disease. In infective endocarditis it is unusual. Serofibinous pericarditis is characteristic of rheumatic heart disease and tuberculosis. A glance at Chart 3 in which the frequency of pericarditis in rheumatic heart disease is compared with that in the infective endocarditides is striking. (Unshadowed areas in each column represent adherent pericardium.) Pericarditis in infective endocarditis is not infrequently suppurative, never in rheumatic carditis.

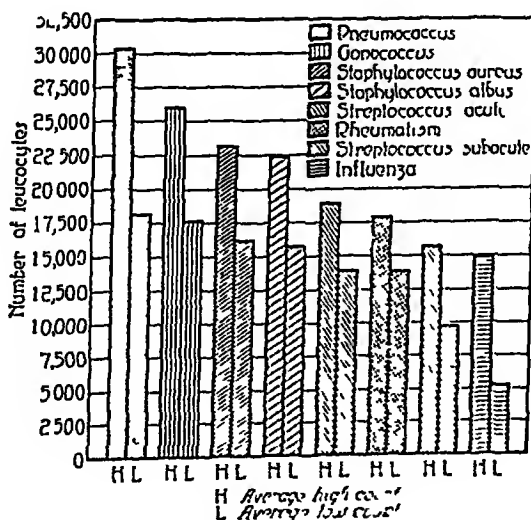


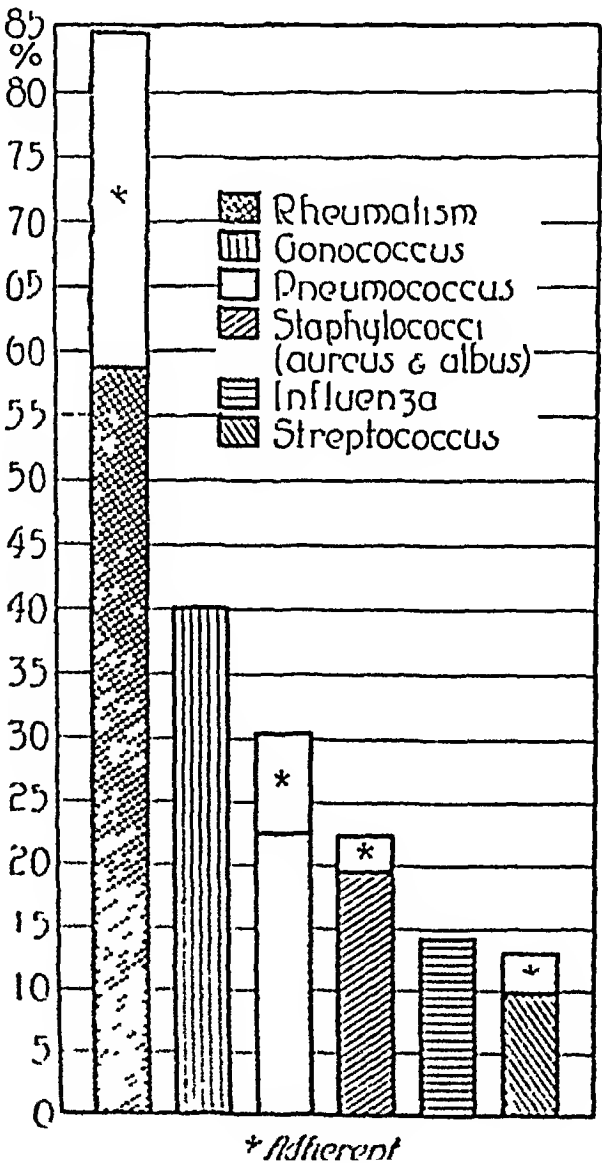
CHART 2 Acute and subacute rheumatic and bacterial endocarditis. Average leucocyte counts—high and low (From Edinb Med Jr 1931, n s XXXIII 263)

Streptococcal endocarditis is that form which is most likely to be mistaken for rheumatic heart disease In 186 instances of streptococcal endocarditis unassociated with acute rheumatic changes serofibrinous pericarditis was observed in little over 4 per cent

The acute myo- and endocardial changes of rheumatism are anatomically characteristic The perivascular Aschoff bodies are generally easily to be distinguished from the relatively

unimportant areas of round cell infiltration in infective endocarditis The acute verrucose vegetations on the valves and the roughening and fibrinous exudate in the outer part of the left auricle, so characteristic of rheumatic heart disease, are associated with subjacent intravalvular and sub-endocardial inflammatory changes which are distinctive

Rheumatic endocarditis is clearly a reaction to focal subendocardial necrotic and inflammatory changes



The distribution of the valvular lesions in rheumatic heart disease is characteristic. The overwhelming frequency of involvement of the mitral, and secondly, of the aortic valves is apparent in Chart 4 which illustrates the distribution of the valvular lesions in rheumatic endocarditis compared with that in the various infective endocarditides. The relative frequency of tricuspid involvement is interesting but the tricuspid involvement, though common, is usually not extensive and is rarely seen apart from mitral disease. The similarity between the distribution of valvular lesions in rheumatic and streptococcal disease is apparent.

These figures relate only to the distribution of *acute* lesions at necropsy. Among over sixty instances of rheumatic heart disease dead with acute

valvular changes, every one showed acute or chronic disease of the mitral valves and 83 per cent of the aortic. Affection of the pulmonic valves is very rare.

Cultures from the circulating blood are usually sterile, an important diagnostic point in doubtful cases. Occasionally, streptococci may be recovered. These are usually non-hemolytic and not found in large numbers or constantly, sometimes only in anaerobic tubes. That there may be exceptions will be mentioned later.

Rheumatic endocarditis, then, is a single feature of a well defined disease picture recognizable usually clinically and anatomically.

The striking characteristics of rheumatic heart disease are its prevalence in early youth, notably in the first two decades, the frequent insidiousness of

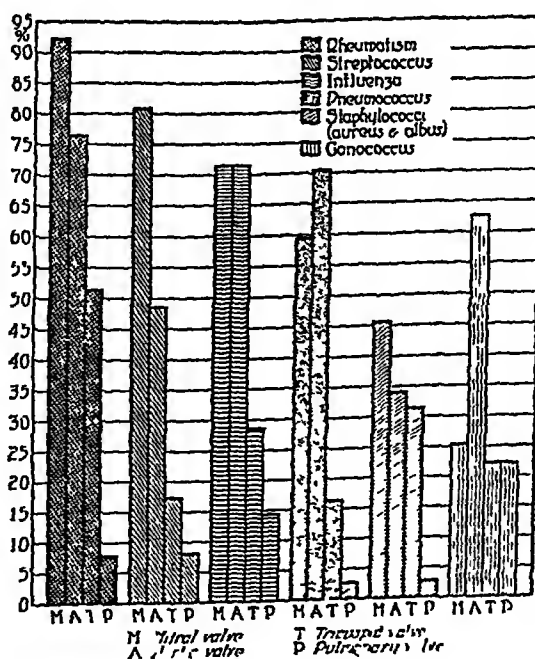


CHART 4 Acute and subacute endocarditis. Proportional involvement of individual valves. (From *Edinb Med Jr*, 1931, n s, xxviii, 253)

its onset and course, its striking tendency to chronicity through recrudescences and recurrences, its evolution into the characteristic chronic valvular heart disease, its common association with fugitive non-suppurative polyarthritis and chorea, the frequency of serofibrinous pericarditis ending in an adherent pericardium, the characteristics and distribution of the valvular, vascular and widespread myocardial changes. It is notable anatomically and pathologically for the circumstance that the non-suppurative serosities, as well as the relatively benign rheumatic endocarditides appear at the outset to be connected with subjacent periarticular, sub-endocardial or sub-pericardial changes. The process does not originate on the surface.

The most important differential clinical characteristic of rheumatic heart disease is that it leads to death through myocardial failure owing to damage to muscle, valves or pericardium resulting from the immediate effects of acute inflammatory changes or more commonly to the prolonged influence, often largely mechanical, of deformities incident to the scarring of healing lesions. Even in acute rheumatic fever with symptoms of a grave intoxication the fatal issue is usually preceded by myocardial insufficiency with dilatation and congestive failure.

In *infective endocarditis*, on the other hand, the earliest changes take place on the surface of the endocardium appearing as small, soft vegetations picked with bacteria along the lines of contact of the valves. At the base of these vegetations there is necrosis and a spreading inflammatory

process which, according to the malignity of the infection and the resistance of the individual, leads to a more or less rapid destruction of the subjacent tissues. Implantation of the infection may follow on spots where the thrombi come in contact with the neighboring heart wall. From the agitated thrombi emboli are commonly distributed by the blood current. These embolic phenomena are among the most characteristic symptoms of infective endocarditis especially of the subacute and chronic forms. Renal embolisms may be so extensive as to result in pain and obvious hematuria or they may be recognized only by occasional showers of red blood corpuscles found microscopically in the urinary sediment. Embolism of the spleen is apparent through the pain and tenderness caused by overlying peritonitis. Cutaneous and subcutaneous embolisms result in phenomena, all the way from tiny petechiae to larger ecchymoses showing a white centre and an hemorrhagic border, or larger swollen cyanotic areas which are very tender. The little tender, cyanotic spots in the pads of the fingers or toes (Osler), and the larger like areas in the soles of the feet and the hands (Janeway), are almost diagnostic*. Small longitudinal painful hemorrhages under the fingernails (Horder) are frequent. Cerebral embolism with hemiplegia is very common, and embolism of larger vessels may result in peripheral gangrene. Mycotic aneurysms are frequent.

*These, as have been pointed out by a number of observers, may be dependent on occlusion of capillaries or smaller vessels by swelling and proliferation of endothelium rather than by embolism.

The character and symptoms of infective endocarditis vary greatly according to its etiology. Infections with *Streptococcus haemolyticus*, *Pneumococcus* and *Staphylococcus aureus* are notably acute and rapidly fatal; the lesions, ulcerative and destructive. Infections with *Gonococcus* or *Staphylococcus albus* which are rare, although the lesions are almost equally destructive, are somewhat less malignant as a rule and a little less acute in their course. Gonococcal endocarditis ends sometimes in recovery. Endocarditis due to more attenuated streptococci or more rarely to the Pfeiffer bacillus pursues often a subacute or notably chronic course lasting sometimes upwards of a year.

The more acute forms of bacterial endocarditis are not often confused with rheumatic heart disease. The valvular lesions are commonly unrecognizable and excepting in those acute ulcerative affections where there is an extensive destruction of tissue, the phenomena are essentially those of a rapidly fatal acute septicæmia hastened generally in pneumococcal infections, by meningitis. It is the more subacute and chronic bacterial endocarditides due, in our series of 121 cases followed to a fatal termination, generally to an attenuated streptococcus (74.1%), gonococcus (10.8%), or Pfeiffer's bacillus (7.5%), which may simulate rheumatic heart disease.

In addition to the embolic phenomena already referred to, these subacute and chronic infective endocarditides have certain characteristic features—the insidious onset, the long, moderate, remittent or intermittent fever, which, indeed, may, for considerable periods

of time, be almost absent, the gradually progressive secondary anemia, the leucocytosis of about the same or a little less intensity than that observed in rheumatic heart disease, the splenic enlargement, the Hippocratic fingers, a curious brownish-grey *café au lait* complexion (Libman), the gradual development of a glomerulonephritis, usually regarded as embolic, with the appearance of albumen and red blood corpuscles and casts in the urine, and eventually of edema and evidences of renal insufficiency. Cultures from the blood in a great majority of instances yield non-hemolytic, green-growing streptococci in gradually increasing numbers. Subacute *infective endocarditis is usually fatal* after a period of from a month or two to a year or even more.

The terminal stages are generally those of a grave septicæmia. The element of myocardial insufficiency was striking in only a quarter of ninety-nine fatal cases followed to a termination. Auricular fibrillation, not uncommon in rheumatic heart disease, is rare. The distribution of the lesions is very similar to that in rheumatic heart disease, for the simple reason that subacute streptococcal and influenzal endocarditis is found generally (70 per cent of our streptococcal, all of our eight influenzal infections) on valves or mural endocardium the seat of previous rheumatic heart disease.

In two respects subacute and chronic vegetative endocarditis and subacute rheumatic heart disease are similar. (1) The distribution of the lesions, commonest on mitral and aortic valves, (2) the common sub-

acute course But while in *rheumatic fever* the intoxication as a rule is not very great, the anemia not very pronounced, and embolic phenomena are absent, in *infective endocarditis*, general constitutional symptoms, fatigue, anorexia and progressive anemia are striking and embolic phenomena are common Osler's phenomena in fingers and toes are almost pathognomonic Nephritis, rare in rheumatic heart disease, generally appears in infective endocarditis Splenic enlargement is rare in the former, the rule in the latter Cultures from the blood are usually sterile in rheumatic heart disease, generally positive in infective endocarditis

The termination of subacute rheumatic heart disease may be in death from myocardial insufficiency but is usually in recovery with the establishment or aggravation of an already existing chronic valvular lesion Subacute infective endocarditis is generally fatal, the terminal symptoms being those of a grave septicemia and nephritis Signs of myocardial failure are usually unimportant

There are certain exceptions, however, to those rules. (1) *Now and then non-hemolytic streptococci are cultivated from the circulation in rheumatic fever* Usually positive cultures are only occasional and bacteria are obtained in small numbers I have seen two instances, however, of rheumatic fever of three or four months' duration in each of which, among a number of negative results there were three positive cultures of streptococcus viridans In each of these instances, the youth of the patient 14 in one (Tredway's case*), 19 in the

other (Ruffire's case), the absence of embolic phenomena, the lack of a grave general intoxication, the absence of splenic enlargement, even in the presence of repeated positive cultures, led to a correct diagnosis; in each instance the patient recovered In neither of these cases were the arthritic symptoms important (2) Recovery from infective endocarditis is probably not altogether so rare as is generally thought On this Libman especially has insisted Few pathological anatomists and few clinicians who pass the hours that they should in the pathological laboratory are unfamiliar with the irregularly scarred and deformed valves which could scarcely be due to anything else than past vegetative endocarditis It is difficult, indeed sometimes impossible, to distinguish convalescence from vegetative endocarditis where the bacteria have disappeared from the blood, from a rheumatic heart disease This or the absence of positive blood cultures, would certainly have been impossible in Perry's† remarkable instance of gonococcal endocarditis with recovery which I had the good fortune to see on several occasions

(3) It must be remembered that in rheumatic heart disease with auricular fibrillation extensive peripheral embolisms may follow the dislodging of bits of thrombi in the auricular appendage Multiple cutaneous, renal

*T Palmer Tredway Endocarditis and pericarditis with blood stream infection of *Streptococcus viridans*, Penn Med Jr, 1930, xxxiii, 389

†Perry, M W Gonorrhoeal endocarditis with recovery, Am Jr Med Sc, 1930, clx, 599-605

and splenic embolisms under such circumstances may, as I have seen, on several occasions, give rise to a rather confusing picture. Diagnosis may indeed be impossible.

(4) Such embolisms may occur in chronic rheumatic heart disease without fibrillation from the formation of mural thrombi in the left auricle. Of this I have seen one striking example.

The distinction between infective and rheumatic endocarditis though usually easy, may be difficult. One should not forget that it may be a delicate question which, like all other clinical problems can rarely be settled by the laboratory alone. It is well to re-

member that in subacute rheumatic heart disease mural thrombi may form without auricular fibrillation, giving rise to peripheral emboli very suggestive of vegetative endocarditis, that non-hemolytic streptococci may occasionally be obtained from the blood during acute rheumatic carditis, and, now and then, on several occasions, that a diagnosis on the one hand of rheumatic carditis or on the other hand of infective endocarditis cannot be made without a careful consideration of all the evidence, that a fatal prognosis in the absence of immediately threatening symptoms need never be made in either affection.

A Theory of the Causation of Cardiac Pain*

By ALEXANDER LAMBERT, M.D., *Professor of Clinical Medicine,
Cornell University, New York City*

AN unsolved problem in medicine stands as a challenge to every physician, and cardiac pain has long stood in this position. It is therefore with peculiar pleasure, and with keen appreciation of the compliment, that I accepted your Chairman's invitation to offer you some heretical opinions concerning its causation

The most recent reviews of Angina Pectoris by Obendoeffer, Kirch and Edens express the almost universal medical belief that cardiac pain is caused by a spasm of the coronary arteries. But this spasm is an unproven theoretical assumption brought forward years ago by Nothnagel. Huchard collected over sixty explanations of cardiac pain, and in some of these it is even claimed that the pain is due to spasm or anemia of cardiac muscles, forgetting that only stimulation of nerves can produce pain.

The nervous system for the heart and its reflexes belongs to a very ancient mechanism. The heart, unlike the kidneys, does not develop segmentally, but originating in the distal portion of the head descends longitudinally. Its nervous system is derived from the autonomic nervous

system, and is obtained from both the sympathetic and cranial portions.

The efferent nerves to the heart are derived from the vagal as well as the sympathetic system, but the afferent sensory nerves belong only to the sympathetic portion. The cardiac vagal system does not carry fibers for pain, its afferent nerves carrying depressor and other vasomotor fibers. The afferent sensory fibers, passing chiefly through the stellate ganglia, join by the rami communicantes the posterior spinal nerve roots, and traversing their ganglions to the spinal cord pass upward by the spinothalamic tract through the midbrain to the centers for the autonomic nervous system in the hypothalamus in the caudate end of the diencephalon.

To appreciate clearly the ancient reflex mechanism controlling the heart, and through the break down of which pain is produced, it is necessary to review briefly some of the physiology of the autonomic nervous system, and that is best done by quoting Cannon's interpretation of it. In general the cerebrospinal nervous system furnishes the discriminative consciousness localizing internal sensation or external danger, and presiding over the action of the skeletal muscular system, makes and carries out the choice of fight or flight. Through the action

*Presented at the Baltimore meeting of the American College of Physicians, March 23, 1931.

of the autonomic nervous system, on the other hand, are furnished to the cerebrospinal nervous system, and skeletal muscles the supplies of sugar, oxygen and adrenal energy sufficient to maintain successfully the choice to fight or flee

The sympathetic portion of this system differs from the cranial and sacral portions, in that the outlying ganglia are so placed in the sympathetic portion that the nerves going through them give fibers to each successive ganglion before the nerve is finally distributed to the viscera. The cranial and sacral systems however, have their outlying ganglia in the viscera themselves. This, as Cannon points out, produces a generalized effect over all the viscera in any sympathetic discharge, while in cranial and sacral discharges of energy the stimulation can easily go to a single viscus to perform a special function without involving any other viscus. As for example, a rise of blood pressure from the general sympathetic stimulation involving the whole splanchnic system, produces a general bodily effect while the stimulation of the cranial portion to increase the tone of the intestines does not simultaneously slow the heart.

Moreover, in those viscera to which two portions of the autonomic system are distributed, the action between the sympathetic and the cranial, or sacral portions are in opposition to each other. For example, in the heart the sympathetic fibers are the accelerators and the dilators of the blood vessels, while the cranial or vagal fibers are the inhibitors of the heart action, and the constrictors of the blood vessels, and

this interchange of opposing action produces the even functioning of the heart and its instantaneous reply to varying demands for increased output.

In general it may be said of the three divisions of the autonomic nervous system that the cranial takes part with the sympathetic in the functions of respiration, circulation, digestion and absorption, the sacral portion with the sympathetic controls the elimination of the waste of the body, through emptying of bladder and rectum and those functions included in racial continuation.

The sympathetic portion secures by its general reactions the delicate balance of the body between its internal and external relations, that is, to use Cannon's phrase, in preserving the homeostasis of the body. Through its special hormone, adrenin from the adrenal glands, the sympathetic system increases and prolongs its own action.

Through this sympathetico-adrenal action the heat loss and heat production of the body is regulated, and the evenness of the bodily temperature is preserved. Through this mechanism the acid-base equilibrium is maintained, and the blood sugar for muscular exertion is prevented from falling to a dangerous degree. The circulatory adjustments, constriction of the splanchnic vessels with rise of blood pressure, acceleration of the heart, discharge of extra corpuscles from the spleen, with increased distribution of extra oxygen, and facilitation of the respiratory processes are all made by means of the sympathetico-adrenal system. Besides these physical and chemical ad-

justments, there are some nervous reflexes involving the sympathetico-adrenal system, which react intensely on the heart and general circulation. Bard has demonstrated that the center of the autonomic nervous system is located in the ventral portion of the caudate end of the hypothalamus.

Animals with their cerebral cortex removed, but with the hypothalamic center intact, still react with purposeful actions, and show prolonged periods of sham rage to slight irritations. It is evidence of emotional reaction with all inhibitions from the cortical centers removed, and the physical symptoms as in cats, of the bristling of their hair over the entire body and tail, their growling, snarling, spitting, anger, and clawing and endeavoring to scratch and run away, often with defecation and micturition, show the intensity of the general discharge from the sympathetic system. It is the evident counterpart of the blind rage of the human young in their fighting, biting, shrieking anger from a loss of cortical control. These are excellent examples of the discharge from the central nervous center, through the sympathetic system to its peripheral effectors, the skeletal muscles and viscera.

Cannon has conclusively demonstrated that any high degree of excitation in the central nervous system, whether felt as anger, terror, pain, anxiety, joy, grief or deep disgust, may rouse the sympathetic system to activity, and affect in a stereotyped fashion the functions of organs which that system innervates.

Many of the reflexes of angina pectoris and cardiac pain occur through this neural mechanism, the attacks of angina pectoris being particularly susceptible to emotional origin.

Beginning with the cardiac reflexes in the early stage of muscular exercise, it is the sudden exertion, as walking against the wind, or up a slight grade, which is often the earliest occurrence to inform a patient that his heart can give him pain. Probably the first reflex action from exertion is the increased depth and rapidity of respiration, and this is followed by a conscious reflex from the higher nervous centers, which quickens and deepens the respiratory flow. This starts the necessary supply of increased oxygen, and with the bellows effect of the chest, increases the venous flow into the heart as the skeletal muscles add their increase of blood, going to the heart through the large veins. There is a rise of capillary and venous pressure, and the Bainbridge reflex occurs in the right auricle; i.e., as the increased venous blood distends the auricle, the vagus nerves around the great veins are inhibited and the accelerators are stimulated so that the rate of the heart increases in proportion to the venous return, and the blood is hurried on through heart. The increase of CO_2 and the lack of O_2 also accelerate the heart.

The anoxemia greatly increases the coronary flow. With the general muscular exertion there is an inhibition of the splanchnic area, and a general rise of arterial blood pressure in the body. As blood pours into the ventricles, there is a stretching of the myocardial muscles, with an increased output per

beat of the heart Both the rise of aortic pressure, and the increased cardiac output greatly increase the coronary flow through the action of Anrep and Segal's coronary reflex, which is a reflex diminution of tone of the vagal vasoconstrictor fibers producing an increased coronary flow The rise of CO_2 tension and the H-ion concentration of the blood also add to the increase of the coronary circulation In normal vigorous cardiac contraction the coronary vessels are filled and emptied with each contraction of the heart, and during each beat of the heart the coronary flow varies practically between empty vessels and well-filled flowing circulation The inflow into the coronary vessels occurs only during the diastolic period, being practically stopped in vigorous healthy hearts during the systolic compression of the vessels by the myocardium These physiologic details are probably tedious to you, but their definite picture is necessary to appreciate the cause of cardiac pain, because it is through the breakdown of the normal physiologic processes that cardiac pain is produced

It is important to remember that the blood supply of the first portion of the aorta is only from both coronaries which form the vasa vasorum of this portion of the aorta, so that the blood supply of the ascending portion of the aorta and of the heart is from the same vessels

Spiegel and Wasserman have shown definitely that the pain from the aorta follows the same pathways as pain from the heart

Singer has demonstrated that eradication of both stellate ganglia makes

insensitive all cardiac and aortic tissues as far as the left subclavian artery

Dogiel demonstrated that the sensory nerve endings of the coronaries and of the aorta and of the blood vessels in general, lie in their adventitial coat

Odermatt in studying the sensitiveness of blood vessels has clearly shown that some arteries are sensitive to ligation, and small arteries more so than large ones

Bazett and McGlone have shown that puncture of the radial is more painful than that of the brachial, and that the pain is a dull aching generalized pain, difficult to locate, and difficult to bear, causing a sudden sensation of warmth with profuse sweating, sometimes accompanied by nausea, and in some individuals by a desire to defecate, and often followed by coldness, faintness and actual loss of consciousness

Odermatt found also that arteries that are sensitive to ligation are also sensitive when their adventitia is stretched or distended, that is, the stretching or distension of these same arteries produces pain, and it is by distension and not by contraction that pain arises

Spiegel and Wasserman have shown also that stretching of the aorta produces intense pain

Singer has demonstrated that an acute ischemia of the cardiac muscle is without any painful reaction in the experimental animal, and that the endocardium and cardiac muscle are completely refractory towards chemical, mechanical and Faradic irritation The pericardium and epicardium are definitely sensitive to mechanical and

chemical irritation, but Faradic irritation provokes little or no reaction. The sensibility of the coronary vessels is dependent on the intactness of the adventitia, which possesses a strong mechanical and chemical sensibility. The aorta is always but feebly sensitive to Faradic irritation; it is only mildly sensitive to chemical inflammatory irritations, but to mechanical pinching and pulling and stretching, the aorta is strongly sensitive. Here also the sensibility depends on the anatomical intactness of the aortic adventitia, but sensitiveness to pain on the part of the media and intima of the aorta could not be demonstrated.

Clinically we are aware that sudden rises of blood pressure may be accompanied or followed by an attack of cardiac pain. Cardiac pain is, however, not dependent alone on blood pressure, for pain occurs with low blood pressures, or with high blood pressures, and Bayliss has definitely stated that the stimulation of any afferent nerve, except the depressor nerve of the heart, will cause this rise of blood pressure. The depressor nerve rises from the heart and aorta, and passes up to the vagus. There is a good deal of discussion as to whether or not this is present in human beings, but the work of Vitti shows definitely that in the majority of mankind this nerve is present, and passes upward separately or in the main stem of the vagus to the superior laryngeal nerve. Its function is to regulate the blood pressure by bringing about a general fall of pressure, and to reduce the blood pressure when it rises to too great a height.

Clinically cardiac pain arises after the period of healthy athletic youth has passed, and the degenerations of senescence have begun, when the heart and its vascular system have become permanently damaged, when the heart has lost its power of instant vigorous response, and its ability to regain its normal functional vigor. It is in this period of senescence in the fifties and sixties that angina usually occurs. If it occurs earlier, it is through premature disease of its tissues, and the inability of its normal reflexes to bring about the normal action and equilibrium between its muscular function, and its own vascular supply.

As the myocardium degenerates there is an increasing dyspnea on exertion, and there finally comes a time when the degenerated myocardium can not contract with adequate vigor to drive on the increasing blood coming into the heart from exertion. The myocardial muscles stretch to increase the output per beat, but can not contract with sufficient vigor to accomplish it. For a while an increased heart rate per minute may act as a substitute for increased output per beat, but there comes a time when the lack of output per beat ceases to stimulate the reflex to cause increased coronary flow, and the heart is in the condition of dependence for its coronary flow on increase of blood pressure. The degenerated muscle cannot contract vigorously enough to empty out the heart, nor clean out its own coronaries. With the incompetent cardiac muscle there occurs an increasing vascular congestion, and finally dilatation of the coronary arteries by which stretching of the adventitia is

produced from over distension of the diseased arteries, and pain is the result. This pain arises from stimulation of the afferent nerve endings in the adventitia of the coronary arteries, and the pain persists until the coronary circulation can recover itself through increased muscular action of the myocardium, or diminished inflow of blood into the heart brings relief.

When the pain arises from the first portion of the aorta, the mechanism of its causation is different. With an aortitis and diseased aortic wall, or with inflammatory processes around the vasa vasorum of the adventitia which press on the sensory nerve endings, any sudden increase of blood pressure in the aorta which some emotion may cause, which any sudden demand for increased cardiac action will produce, will cause an increased stretching of the aortic adventitia sufficient to produce pain, but not sufficient to cause reflex action of the depressor nerve to occur, and by lowering of blood pressure bring about a cessation of the stretching of the adventitia. The giving of the nitrites instantly produces a general fall of pressure, a general relaxation of the vascular muscularis, and the painful stretching ceases. The action of the nitrites is substituted for that of the depressor nerve.

Clinically in attacks of angina pectoris the pain is accompanied with symptoms from widespread reflexes. There is at times lacrimation, salivation, pupillary dilatation, general intense sweating, nausea, and vomiting, or intense belching of gas. There is not infrequently a desire to micturate, and Olser and others report testicular

pain. The observations of Bazett and McGlome already quoted, demonstrate that the aching pain from arterial puncture is often followed by similar reflexes, such as a sudden sensation of warmth followed by sweating, and then coldness, faintness and even loss of consciousness. In some individuals there may be nausea at times, and a desire to defecate.

The analogy of the clinical picture of certain attacks of coronary thrombosis and the sequence of reflexes from arterial puncture is apparent. It would also seem to indicate that the pain of angina, as well as of coronary thrombosis, is of vascular origin originating in the afferent nerves of blood vessels, passing to the general autonomic center in the hypothalamus. The intensity of the pain causes an intense general sympathetic discharge producing a reflex action in both the cranial and sacral portions of the autonomic system. The pain simultaneously manifests itself through the afferent connections of the sympathetic system with the cerebrospinal nerves, being felt and localized in cortical consciousness as present in the familiar positions on the trunk and down the left arm. These widespread reflexes produced by the diffused discharge of the sympathetic system indicate how ancient is the mechanism of the cardiac pain, and to explain it satisfactorily we must consider the nervous mechanism of the heart before the neopallium was present.

The theory here offered is further supported by the results from the operations of sympathectomy performed to eradicate the pain in angina, or the occurrence of the whole anginal

symptom complex. Hesse reviewing 135 cases of various methods of sympathectomy, concludes that extirpation of the superior cervical ganglion was successful in 62.57 per cent but cutting across the superior cervical ganglion just above the origin of the great cardiac nerve, and removing the cervical sympathetic cord to just above the inferior cervical ganglion, gave 80 per cent of successes. Removing the cervical chain of ganglia with the stellate ganglion was successful in only 56 per cent. Cutting off the pathway for the vasomotor reflexes in the superior cervical ganglion is therefore more successful than obliterating the afferent and accelerator fibers through the stellate ganglion. The most successful operation obliterates the vasomotor pathway, plus some of the afferent fibers, passing through the middle sympathetic nerve and ganglion, and prevents the reflex action of the general sympathetic discharge from culminating in an attack of angina.

How does this theory of vascular distension instead of vascular contracting spasm explain better the puzzling clinical manifestation of cardiac pain? Cardiac pain is brought about by increased muscular exertion as we have just shown. It is also produced by going into a cold room or getting in between cold sheets. Cold produces contracting of the skin vessels, a sudden increase of blood pressure, a stimulation of the sympathico-adrenal action with adrenin secretion and acceleration of the heart action with quickening of the metabolism to increase heat production. Cold therefore produces increased cardiac demands for which the myo-

cardial muscles may be inadequate, and pain occurs as above.

In pernicious anemia, or in other severe anemic conditions, cardiac pain sometimes occurs. In anemia the coronary circulation is at times increased five fold above normal, but the myocardial muscles suffer in their nutrition. The diseased coronaries are already distended with blood, and with an inadequate myocardial contraction pain is all the more quickly produced. But following blood transfusion the pain ceases, because the coronary flow returns to normal proportions and with a better nourished myocardium, improved in the vigor of its contraction, the coronary distension ceases, and cardiac pain disappears.

Following acute infectious diseases such as influenza there is an acute myocardial degeneration in a subject with diseased coronaries, and there is an acute myocardial breakdown producing the coronary distensions and pain.

The cardiac pain following nicotine intoxication apparently arises from paralysis of the synapses between the preganglionic sympathetic fibers and the postganglionic fibers in the sympathetic ganglia.

Woolhard has brought forward evidence showing that the sympathetic nerve fibers alone supply the ventricular muscles. The sympathetic accelerators influence the conductivity of the cardiac impulse and the contractility of the muscles. When the nicotine poisoning is sufficiently intense there is paralysis of the accelerators which produces the same inadequate myocardial contraction as degeneration of the muscle. When the nicotine is removed the pain ceases. The use

of tobacco in some patients increases the frequency and intensity of the anginal attacks, as the accelerator paralysis is added to the already existing myocardial degeneration

Anger, fear, joy or pain, or any intense emotion, causes, as we have seen, an intense general sympathetic discharge from the hypothalamic autonomic center, and causes, as Cannon has shown, a secretion of adrenin and increased blood pressure and acceleration of the heart's action, which may make increased demands on an inadequately contracting myocardium, with the cycle of events as already described bringing on the undue stretching of the aorta, or the distension of the coronaries and cardiac pain

In coronary thrombosis or infarction the pain can be produced either by causing inadequate myocardial contraction, or by causing coronary distension in the obstructed blood vessel proximal to the obstruction. If there is sufficient collateral circulation in the coronaries to prevent the vascular distension, pain would not occur

The theory of cardiac pain here presented seems also to explain the incongruous pathologic anatomy found in post mortem examinations of those patients dying in an attack of angina pectoris, or those who gave a history of having suffered cardiac pain. Aortitis, especially luetic aortitis, has been found with a history of previous pain, and frequently found with a history of no pain. Coronary arteriosclerosis with distended vessels, or with thickened and occluded arteries, and with or without calcification, has been found with histories of pain and anginal attacks, and also with definite histories of no pain. Coronary thrombosis and

infarct occur also with and without pain. Aortitis with or without coronary disease and coronary disease with normal aorta has caused many discussions of the causation of cardiac pain

Luetic aortitis, beginning as it does in the vasa vasorum, more frequently seems to cause pain than aortitis from other causes. Kutchera Aichbergen emphasizes the fact that a history of pain is more frequently present with thin walled dilated coronary arteries than with the thickened or calcified vessels. The observation of the writer during the past two years seems to corroborate this opinion. Whatever the cause of arteriosclerosis, the first tissue to degenerate is the internal elastic layer which causes a strain on the muscularis, and a distension of the vessel. As Thoma showed, the thickened intima is a defense reaction to prevent the vascular distension, and to protect the muscularis. Cardiac pain occurs chiefly in the early years of senescence when the arterial degeneration has actively begun in both blood vessels and myocardium, and does not wait till the calcified processes of senility have occurred

It seems, therefore, judging from the evidence of experimental work, that cardiac pain arises in the ancient mechanism of the autonomic system originating in the sensory nerve endings of the cardiac vascular system, and in the wall of the adjacent aorta. This pain occurs when there is an abnormal distension of the adventitial coats of the aorta and coronaries, through the breakdown of reflex mechanisms to which the degenerated tissues of the aorta and myocardium are unable to respond effectively

The Insulin Coefficient, an Improved Method for the Clinical Control of Diabetes Mellitus*

By JOHN R. WILLIAMS, M.D., F.A.C.P., Rochester, N.Y.

THE diagnosis and treatment of diabetes are as yet on an unsatisfactory basis. In advanced cases the diagnosis is easy but in the border-line and doubtful groups a clinical problem is presented which is very difficult of solution. The finding of sugar in the urine to a large group of physicians is *prima facie* evidence of diabetes, although it has been clearly established that sugar and other reducing substances may be found in the urine in a number of conditions other than diabetes.

With the advent of blood chemical methods a few years ago, blood sugar assumed high importance in the diagnosis of the disease. To many physicians a high blood sugar is pathognomonic of diabetes. Adaptations of blood and urine sugar tests such as the glucose tolerance tests have been developed. These examinations as usually carried out are fraught with possibilities for serious error, harm and injustice to the patient. Every year thousands of persons are condemned to a life of dietary restriction and insulin therapy because in a casual examination of the urine a reducing sub-

stance or a sugar has been found which has no disease significance. Numbers of applicants are unfairly denied life insurance for the same reason. It is true that uncontrolled diabetics usually have a glucosuria and high blood sugars, that they also exhibit an abnormal reaction to the glucose tolerance test, but it is also true that a large number of people who have not diabetes will, on occasions, show these same phenomena to a degree which is both disconcerting and confusing. It may be said, therefore, that the prevailing criteria for the diagnosis of diabetes are not very satisfactory.

For similar reasons the guides to treatment which are employed are open to question.

Prevailing Criteria of Treatment in Various Diabetic Clinics

- 1 Fasting blood sugars
- 2 Blood sugars without reference to time of food or insulin therapy
- 3 Reducing substances in the urine
- 4 Grams of glucose per unit of insulin administered
- 5 Normal fasting blood sugar and sugar free urines.

*Presented at the Baltimore meeting of the American College of Physicians, March 21, 1931.

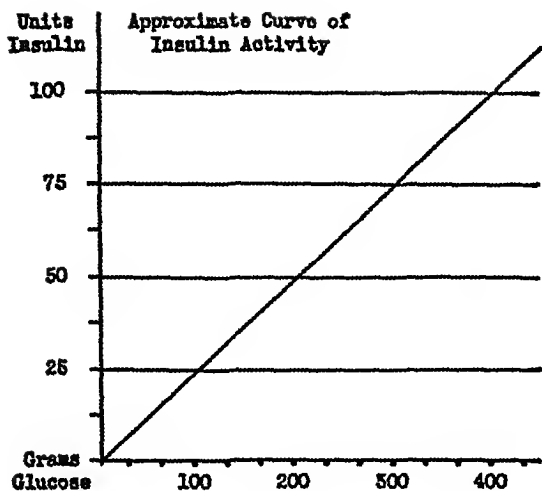


CHART 1

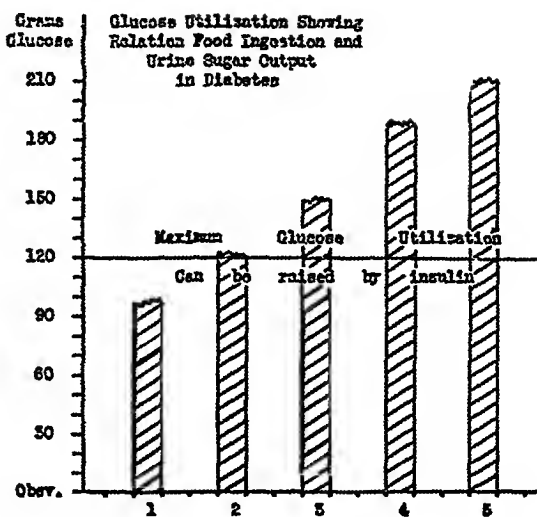


CHART 2

CHART 1 Graph showing approximate curve of insulin activity. The true curve is probably not a linear one, particularly with large amounts of insulin. Within the range of usual clinical application the curve is sufficiently accurate.

CHART 2 Each diabetic patient has a limited capacity to metabolize glucose. Glucose eaten in excess of that amount is eliminated in the urine. There is a fairly definite relation between intake and output. Unutilized glucose may be stored for several days before it is eliminated, therefore clinical observations based on single tests may be inaccurate. In this case it is assumed that the patient cannot utilize more than 120 grams. All above that amount is eliminated as urine sugar.

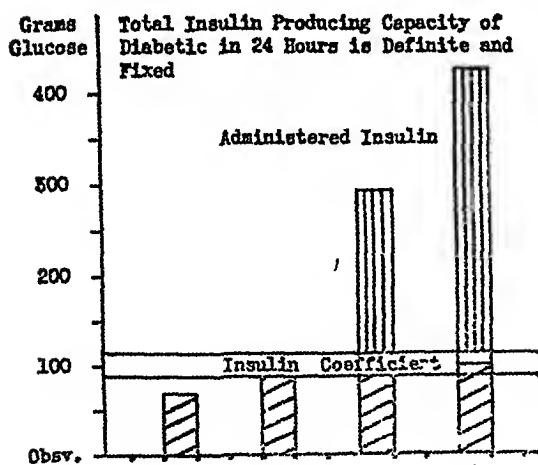


CHART 3

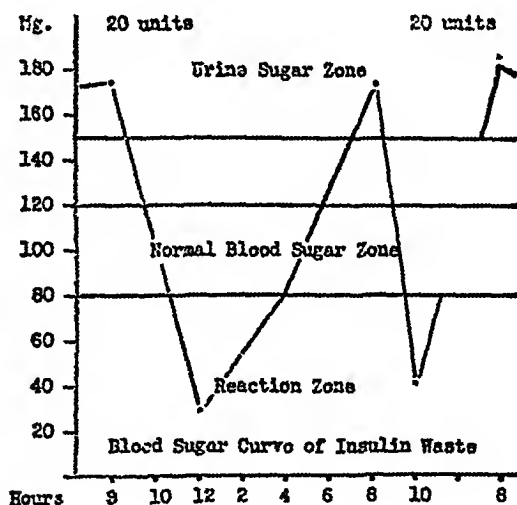


CHART 4

CHART 3 The insulin coefficient in each diabetic is fixed and constant. It cannot be increased by therapy. The ability to utilize glucose can be increased by the supplementary administration of insulin. In this suppositious case the patient is able to utilize only about 120 grams of glucose but when insulin is administered his utilization may be increased to 400 grams.

CHART 4 Blood sugar curve of a diabetic who received two doses of 20 units of insulin daily. Preceding the morning dose he would have sugar in the urine, two hours after it he would have reactions. This phenomenon was repeated in the evening. Insulin dosage which drives the blood sugar down into the reaction zone is wasted.

The blood sugar is a marked variable. While it is usually high in severe diabetes, in many cases it is often low; conversely in mild diabetes it is sometimes high. More important is the fact, which is rarely recognized, that blood sugar is merely a measure of insulin concentration or activity in the blood at the time when the specimen is removed. It is a fluctuating factor and not a constant one as is commonly assumed. Because the blood sugar is high at one hour does not necessarily mean that it will be high all day. One cannot determine the amount of food a patient can utilize in a day by estimating the blood sugar. That information must be gotten in another way, yet it is a common practice for physicians to base their dietary and insulin prescriptions on such data. In short, the blood sugar reveals the intensity of insulin in the blood at a certain time and gives information as to the balance between the previous meal and insulin activity. For this purpose it is valuable.

Qualitative tests of the urine for sugar with copper solutions is another procedure of questionable value. Some of the reagents in common use are so sensitive that they react to other reducing agents than sugar. Even when sugar is present the test is too crude to be of great service. I have seen many patients who have been instructed to follow a program of diet reduction and to increase insulin dosage until the urine became free of reducing substances to these tests. Many of these cases have not had diabetes.

"Grams of glucose per unit of insulin administered" is a step in the right direction but it represents a combina-

tion of factors and does not take into consideration the insulin produced by the patient. Furthermore it creates the impression that the trouble with the diabetic is that he is not able to properly use insulin and that insulin has a variable strength in different individuals, whereas it is well known that diabetes is due to a failure of the pancreas to make insulin in proper amounts and that insulin has a fairly constant strength and so may be standardized.

"Normal fasting blood sugar and sugar free urine" as a guide to therapy are also open to criticism for reasons which have already been stated and also because, as usually employed, they may be very misleading and are not sufficiently definite. The wide use of this procedure as a guide to treatment undoubtedly has much to do with the great variety of dietary procedures in vogue.

Prevailing Methods of Treatment

1. Underfeeding Low fat. Insulin only to advanced cases.
2. High fat Insulin only to advanced cases
3. Balanced slightly restricted diet Diabetic foods Restricted insulin dosage.
4. Diet high in carbohydrates and calories Heavy insulin dosage.

That patients do fairly well on all these widely varying and opposing procedures indicates a great degree of adaptability in the diabetic.

This conflict of opinion and method, both in the diagnosis and treatment of diabetes, suggests to the critical student that more definite methods of diagnosis are desirable and that while

many plans of treatment are useful there is probably one which may be regarded as the optimum. A solution of the problem may be approached by first defining it. The following statements about the disease are quite generally accepted as facts:

Diabetes is due to a failure of the insulin function of the pancreas

There is a direct relation between the amount of insulin produced and the severity of the diabetes

The amount of insulin that an established case of diabetes can produce is quite definitely fixed

If these statements be true, why is not the correct diagnostic procedure to measure the insulin producing function of the pancreas? And if this be done, why is not the amount of insulin the patient is able to make an index of the severity of the diabetic process and a useful guide to treatment? I believe it can be done and that it is a thoroughly practical method of study. It has been employed in our clinic for three years with very satisfactory results. For its successful application it is first necessary to set forth certain

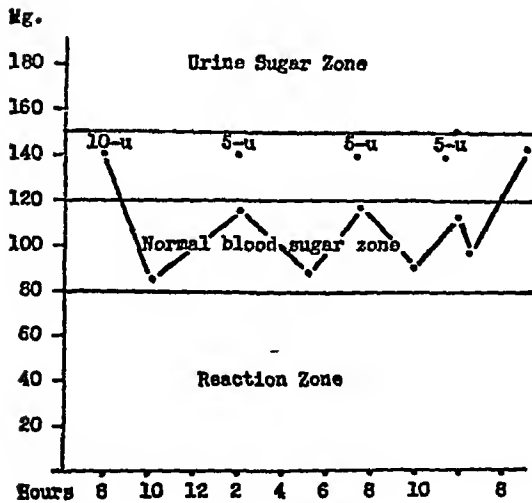


CHART 5

CHART 5 Blood sugar curve of a patient shown in Chart 4. When the insulin dose was reduced, divided into smaller doses and properly spaced, both the glycosuria and the reactions stopped. There was a sharp rise of 15 units in the insulin coefficient. Diabetic patients frequently are greatly helped by rearrangement of the diet and insulin therapy, as in this case.

CHART 6 Showing insulin coefficient graph of improper treatment of a child. This patient carried a persistently high blood sugar and in the endeavor to reduce it the diet was lowered and the insulin dose increased to the point where the coefficient dropped to minus 14. In other words, the patient was wasting a large amount of the insulin that was administered as well as that which he was able himself to produce. He was miserable from reactions and undernourishment. When his diet was corrected and his insulin dose greatly reduced and adjusted, his coefficient rose to 40. This is not an unusual experience with children. The blood sugar is a very unreliable guide to the total glucose metabolism of diabetes.

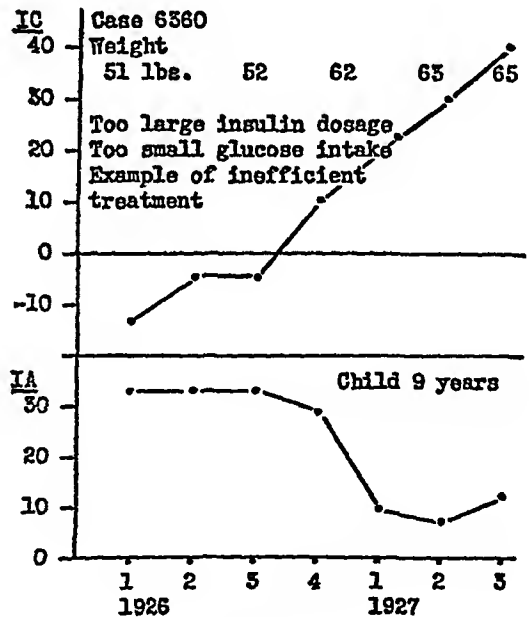


CHART 6

principles of the metabolism of the diabetic

The ability of the diabetic to utilize glucose is fairly constant but slowly declines over a period of months or years. It cannot be increased by eating more food. Insulin therapy increases it. Glucose, in excess of the capacity of the body to utilize it, is excreted as urine sugar. For a few days at a time it may be stored in excessive amounts. For purposes of clinical study it should be assumed that the body derives glucose from all

foods. In our clinic the standard method of approximating the glucose content of the diet is employed.

100 grams carbohydrate yields 100 grams glucose
100 grams protein yields 58 grams glucose
100 grams fat yields 10 grams glucose

Therefore, the glucose content of the diet for twenty-four hours, less the glucose content of the urine for the same period, equals the amount of glucose stored or utilized. If the observations cover a period of five or six days a fairly accurate measure

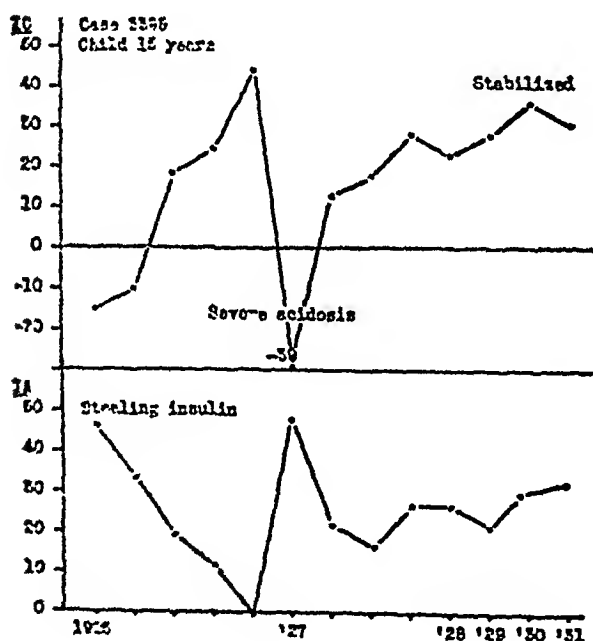


CHART 7

CHART 7 This group shows the insulin coefficient record of a child who began by stealing food. When he was apprehended he tried to conceal it by surreptitiously taking insulin. Several syringes and ampoules of insulin were found secreted in his clothing and room. By supplementing the extra food with insulin he made it appear to us that he was rapidly improving and that less insulin and more food was required. It will be noted that his coefficient rose from minus 15 to plus 45, an astonishing recovery. Accordingly the insulin dose was gradually reduced to the point where it was thought it was no longer needed. At this time his clandestine actions were discovered and effectively stopped by putting him in the hospital under strict observation. The sudden deprivation plunged the patient into coma. Since then he has been co-operative and for three years has been stabilized with an insulin coefficient approximating thirty.

CHART 8 This patient was taken acutely ill with lobar pneumonia. Before the onset of the infection he had an insulin coefficient of approximately 20. He was therefore severe diabetic but was so adjusted as to be practically well. With the onset of the pneumonia his coefficient rapidly dropped to minus 25, which means that larger doses of insulin were given to him, for reasons unknown, were not effective. The action of the insulin was neutralized or partly destroyed, hence the minus coefficient. The fifth observation occurred on the day the fever terminated by crisis, the coefficient rising to 15. After the fever recovered very rapidly and the index rose to its former level of 20.

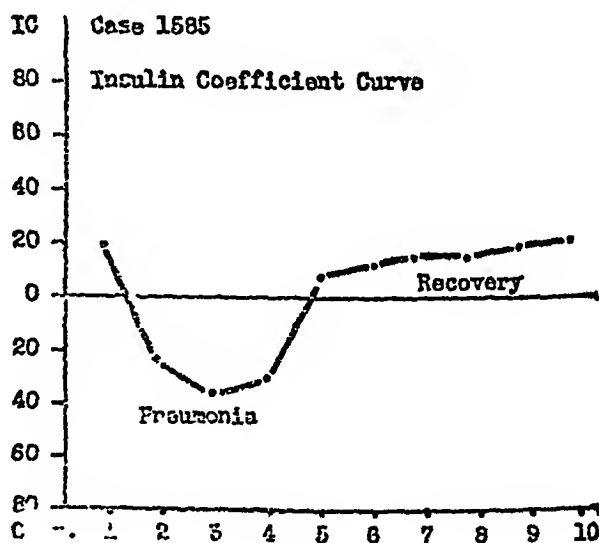


CHART 8

of the ability of the body unaided to utilize glucose will be afforded. The foregoing is essentially accurate if the amount of food ingested is not greatly in excess of the capacity of the patient to metabolize it. Therefore, the first step in the problem is to determine the glucose utilization.

The chief action of insulin is the formation of glycogen from dextrose. One unit of insulin promotes the utilization of approximately four grams of glucose. It is commonly

stated in the literature of the manufacturers of insulin and also by most authors that one unit of insulin will burn 15 to 20 grams of glucose in the body. For several years, in fact, since insulin has been available for clinical use we have made on highly trained, carefully controlled diabetic patients, clinical assays of the product which have been checked by independent animal experiment or assay in another laboratory. Our results almost invariably agree. It may be said, therefore, with confidence, that in the uncomplicated well controlled diabetic one

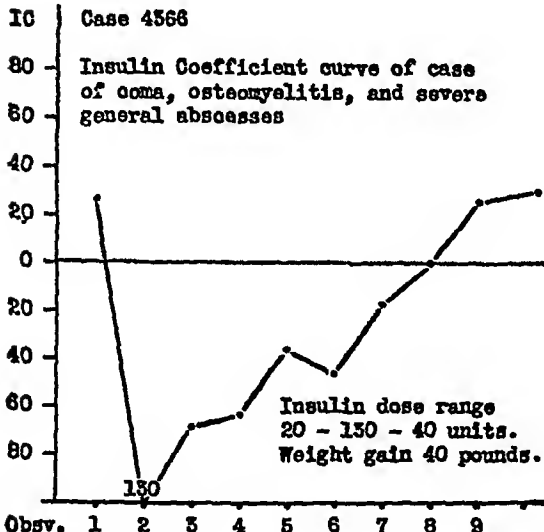


CHART 9

CHART 9 This patient, a male of 28 years, is a severe diabetic with an insulin coefficient of approximately 25. Was taken acutely ill with abscesses and osteomyelitis involving the leg. He was admitted to the hospital in profound coma. 130 units of insulin on the day of admission apparently had little effect on his diabetes. He had a coefficient of minus 130. For several weeks he suffered from large abscesses in various parts of his body. The osteomyelitis in the leg became so severe that death seemed inevitable. Leg amputation was repeatedly urged by counsel. A slowly rising insulin coefficient suggested that the infective disease process was being overcome so operation was deferred. Shortly thereafter the patient made a most miraculous recovery, justifying our faith in the method. The patient within a period of six weeks gained forty pounds in body weight.

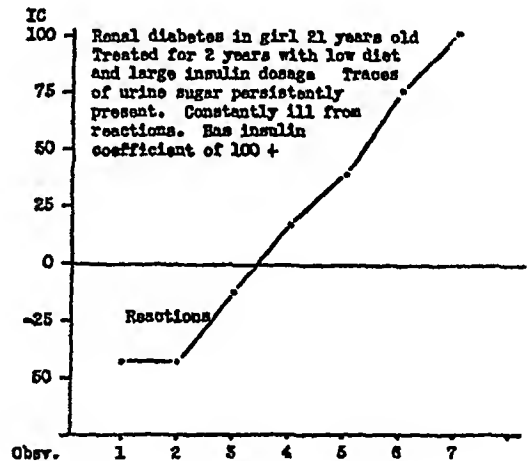


CHART 10

CHART 10 Insulin coefficient graph of a renal diabetic. This peculiar disturbance is frequently treated by strict diets and insulin therapy with distinct harm to the patient. Because traces of sugar were frequently found in the urine for two years this patient was subjected to a rigorous diet and excessive insulin therapy. She was confined to bed for weeks constantly ill from reactions which took the form of a mental disturbance. With discontinuance of the insulin and proper arrangement of diet, the patient's coefficient rose from minus 40 to over 100. In a few weeks she was completely restored to health and has remained so over a period of two years. The writer has seen two cases where mild mental disturbance was directly ascribable to insulin reactions.

unit of insulin promotes the utilization of four grams of glucose. It is not claimed that the function of insulin action follows a linear curve. In all probability it does not. With very large doses the ratio of activity declines, but within the range of clinical application and under ordinary conditions it is approximately accurate.

The maximum amount of insulin which a patient may produce in twenty-four hours is designated as the insulin coefficient. In uncomplicated diabetes it is fairly fixed. After a permanent diabetic state is established it rarely fluctuates more than five units. From year to year in well con-

trolled cases it shows very little change.

Example of Test Case

Diet glucose	160 grams
Urine glucose	<u>40 grams</u>
Glucose utilization	120 grams
$\frac{120}{4} = 30$ units insulin required.	

After studying several hundred patients in this manner the following classification was made on the basis of severity of the diabetic process

Insulin Coefficient of

Normal individual	100 +
Borderline diabetic	75 —
Mild diabetic	40 to 75
Moderately severe	25 to 40
Severe	20 or less

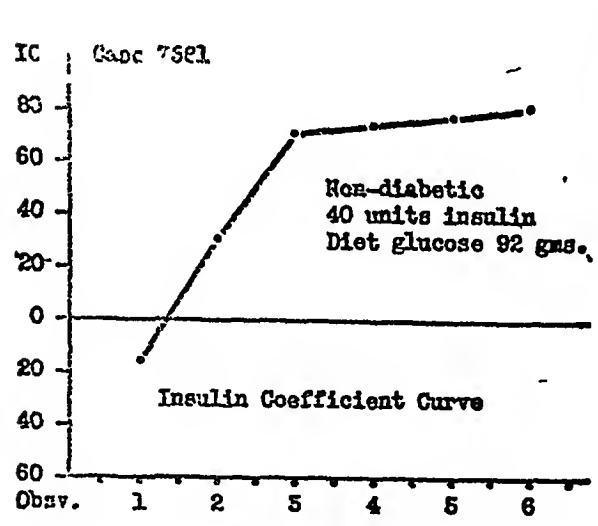


CHART 11

CHART 11 Non-diabetic suffering from a mild psychoneurosis associated with the menopause. Treated for several months on a low diet and large doses of insulin. Erroneous diagnosis based on the occasional finding of a reducing substance in the urine which had no relation to carbohydrate metabolism. Patient was instructed to increase her insulin dose gradually until the urine became clear. Suffered constantly from reactions. Her insulin coefficient under proper dietary regulation rose from minus 15 to over 100 when the tests were discontinued.

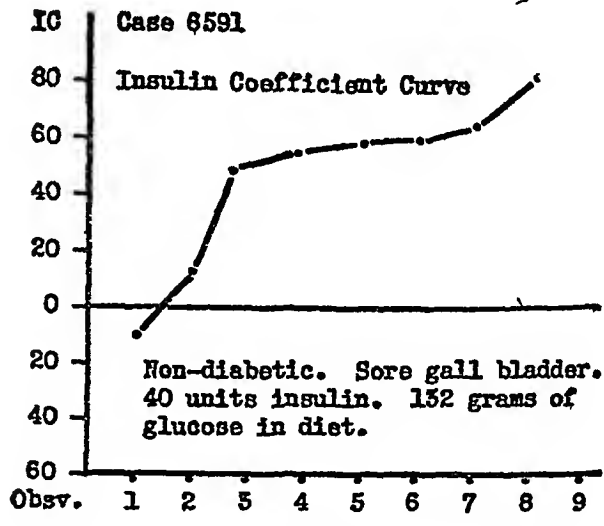


CHART 12

CHART 12 This is the insulin coefficient graph of a non-diabetic with a mild gall bladder disturbance. The patient was treated for one year in an institution on a low diet and large doses of insulin. She suffered constantly from reactions. She has a coefficient above 100. The erroneous diagnosis was based on the occasional finding of a reducing substance in the urine and a questionable blood sugar determination. It will be observed that with proper arrangement of her diet, her coefficient rose from minus 10 to approximately 100. Indeed, the maximum was not reached because of the unwillingness of the patient to eat the excessive food required for the test.

The average normal individual eats a diet which will yield from three hundred to four hundred or more grams of glucose. The amount will vary with the eating habits. The diet of the average temperate eater which will include sugar, bread, cake, fruit, and the common vegetables rich in starch will yield about three hundred grams of glucose. The border-line diabetic who practices little dietary restriction and who is difficult to diagnose usually eats about this amount of food. Such a diet would require seventy-five units of insulin. An individual whose coefficient is less than seventy-five should be regarded as a diabetic. Yet for purposes of diagnosis it is often desirable to carry the diet up to the point where 100 units would be required. It is confidently believed that examinations of this sort, carried on over a period of days or even weeks, in which the insulin coefficient of the individual is carefully determined, is infinitely more accurate and valuable than such unnatural tests as the glucose tolerance, or the taking of sporadic blood and urine tests after special meals. In this connection the fundamental definition of diabetes should be borne in mind. It is a disease in which the ability of the body to utilize glucose is partly lost due to a failure of the pancreas to make insulin in sufficient amount. It is not necessarily a disease of high blood sugar or urine sugar. These are incidental phenomena which commonly occur in diabetes but, also, in other maladies. The real tests are glucose utilization and insulin production.

For purposes of work in our clinic we use the following symbols

$$\begin{aligned} \text{Glucose utilization} &= \text{GU} \\ \text{Insulin required} &= \text{IR} \\ \text{Insulin administered} &= \text{IA} \\ \text{Insulin coefficient} &= \text{IC} \\ \frac{\text{GU}}{\text{IR}} &= \text{IR} \\ \frac{4}{\text{IR}} - \text{IA} &= \text{IC} \end{aligned}$$

An example of a supposititious case would be as follows

$$\begin{aligned} \text{Glucose utilization} &= 120 \text{ grams} \\ \text{Insulin administered} &= 10 \text{ units} \\ \frac{120}{4} &= 30 \text{ IR (insulin required)} \\ 30 - 10 &= 20 \text{ IC (insulin coefficient)} \end{aligned}$$

Frequently one encounters a patient who is getting more insulin than the diet requires. This produces a minus coefficient.

$$\begin{aligned} \text{Glucose utilization} &= 120 \text{ grams} \\ \text{Insulin administered} &= 40 \text{ units} \\ \frac{120}{4} &= 30 \text{ IR (insulin required)} \\ 30 - 40 &= (\text{minus}) -10 \text{ IC (insulin coefficient)} \end{aligned}$$

A minus insulin coefficient suggests a number of explanations

1. The patient may be getting insulin in too large doses which do not synchronize with the food eaten. Since insulin activity usually extends over a period of two to four hours and food digestion and absorption over from five to ten hours, excessive insulin dosage may be lost or wasted.

2. It is well known that infections interfere either with insulin production or activity.

3. Insulin injected into scar tissue may be wasted or it may leak out of the skin along the needle track.

4. The patient may be eating food in excess of that provided in the diet, thus introducing an error in the calculation.

The insulin coefficient method is a most excellent way of checking the

stealing of food which formerly was the universal sin among diabetics, and is even now occasionally practiced. Indeed, in our work we have found the insulin coefficient method of great service in detecting all kinds of errors as well as chicanery on the part of patients. By means of it we determined that a patient was not accurately measuring his insulin, his insistence to the contrary notwithstanding. We found another patient stealing insulin. This individual, a child, had purchased and secreted insulin outfits in various places and would indulge in all sorts of dietary sprees fortifying himself by the indiscriminate injection of the insulin. We have detected concealed and unsuspected infections and have used it as a clinical guide in the care of serious inflammations of various parts of the body, as bones, lungs, abscesses. In this connection it may be said that the insulin coefficient in a diabetic suffering from an inflammation is a more useful and accurate measure of the disease process than are either the leucocyte count or the temperature curve.

In the diagnosis of borderline or doubtful cases the method is particularly valuable. We have had many cases who have been under a strict diabetic regime including insulin therapy, all because traces of reducing substance were found in the urine. In some instances this reducing material was sugar, in others it was not. Many of these cases had coefficients above one hundred. They were not able to eat sufficient food to show impairment in glucose utilization. In the final diagnosis of doubtful insurance risks the method far exceeds in value and

fairness the so-called glucose tolerance test, for while it is true that all diabetics give a positive reaction to this method it is not true that all who react to it have diabetes. Furthermore there is no unanimity of opinion as to the significance of the data that is afforded. Most condemning of all, it is a wholly unnatural procedure. It falsely assumes that because the body is unable to assume a sudden and very unusual load that it is not able to perform the same work if spread over a reasonable time.

In the treatment of diabetes the coefficient method is particularly valuable. The clinician has one guiding rule. He first determines how much insulin the patient can make in twenty-four hours by a careful dietary and urine study covering several days. This becomes the patient's coefficient. If this be low, insulin therapy becomes necessary. The dosage is determined by repeated tests involving the factors of time and quantity of insulin to obtain the highest degree of glucose utilization. The constant endeavor is to raise the coefficient, for by so doing, the most effective combination of diet and hormone action is secured. In these studies it may be discovered that the patient will do best with a different arrangement of diet or insulin dosage than has been employed. Sometimes three or four small doses properly spaced are much more effective than the same number of large doses. Reactions are a sure sign of wasted insulin. In this method the blood sugar becomes a guide to insulin dosage and not to total metabolism. A quantity of insulin which produces an abnormally low blood sugar two or

three hours later is partly wasted. The patient should be kept in that state of balance which will enable him to utilize to the fullest extent the insulin which he produces himself. The body weight is an important factor in the arrangement of the diet. If the patient be undernourished then the diet should be sufficiently ample to correct this factor. If he be obese it should be modified accordingly, the constant aim being to keep the patient practically urine sugar free, with a maximum insulin coefficient and the body weight properly controlled. The method permits the epicurean patient to indulge himself with safety. The pseudo-scientific food and drug fads which have grown up around diabetes can well be forgotten.

It is not claimed that the method is infallible. There are other factors than insulin involved in the diabetic process. In the metabolism of profound coma, insulin often fails to work or acts feebly. Oftentimes in the severe diabetes of childhood insulin response is not in accord with the one to four ratio, but the method, however, is just as useful a guide to helpful therapy as if it were. The insulin coefficient offers a valuable control to clinical research on diabetes, which must be done on the human. There are many unsolved problems. For the great majority of cases, however, both for diagnosis and treatment, in our hands it is by far the best method with which we have worked.

CONCLUSION

The problem of diagnosis in advanced diabetes is simple and presents

no technical or clinical difficulties, but not so with doubtful or borderline cases. At the present time we are depending upon tests of very uncertain value, highly speculative and in a large measure illogical. If diabetes be due to a defect in the total metabolism of the individual, then tests which disclose only a slight transient or inconstant departure from the normal physiology or body chemistry and which are commonly present in other disease states, cannot be regarded as conclusive. The insulin coefficient method directly and accurately measures the capacity of the individual to utilize glucose, therefore its findings are logical and conclusive.

In like manner the criteria by which the diabetic is now dieted and treated with insulin are open to the same objections. They permit of the widest variation in therapy and are not sufficiently definite to make evident which is the best. The insulin coefficient method enables the clinician to determine with exactness the amount of insulin the patient may himself make, whether or not administered insulin is being used efficiently, and whether or not glucose is being properly utilized. Under this plan slightly elevated blood sugars and small amounts of sugar in the urine, while of interest, are of secondary importance. Its great advantage to the doctor is that he has a single guiding rule which gives him an unfailing index to the condition of the patient and for the patient it makes it possible for him to live under the best possible conditions. For these reasons it may be regarded as the optimum method.

The Effect of the Ingestion of Burdock Root on Normal and Diabetic Individuals

A Preliminary Report*

By A. A. SILVER, M.D., and JOHN C. KRANTZ, JR., Ph.D., *Baltimore, Md.*

A *ARCTIUM lappa* or burdock is a coarse biennial weed which grows in Europe, Asia and North America. Early in the nineteenth century, it was observed that the administration of burdock root was beneficial in cases of skin eruptions, gout, rheumatism and calculous complaints.¹ For many centuries it has been utilized in the kitchen of many households and restaurants of the Japanese.² There the root is stripped of its bark and the pulp is sliced, boiled, seasoned, and served as a vegetable much as the occidentals serve parsnips and sweet potatoes. Coincidentally it is interesting to observe that the Japanese have a high racial immunity to diabetes.³ Burdock has enjoyed some reputation as an alterative in constitutional blood diseases. "Burdock tea", designated as *Radix Burdanae* in Germany, has been regarded as an efficient blood purifier. From 1830 to 1910, burdock was recognized by the United States Pharmacopeia. Culbreth⁴ lists its constituents as inulin, a bitter extract, fat, resin, levulose, and cellulose. The drug is indicated, according to this author, as a diaphoretic, diuretic, alterative, and depurative, and

is useful in gout, rheumatism and in dermal eruptions.

In 1851 Bouchardat⁵ observed that levulose was tolerated better by diabetics than glucose, and noted that patients with mild diabetes were aglycosuric when they ate 50 to 100 grams of this monosaccharide per day. Johanson⁶ showed that levulose increased the respiratory quotient more rapidly than did glucose, and that the duration of the elevated quotient was also longer. Straus⁷ recommended a daily diet of 50 to 100 grams of inulin and observed that favorable therapeutic results followed. He found also that inulin was anti-ketogenic and this seemed to indicate that this polysaccharide was absorbed. Tanaka⁸ found inulase in the placenta and in the spleen of warm blooded animals which suggests that this polysaccharide may be split in the intestinal tract by this enzyme. The work of this investigator is substantiated by the experiments of Okey⁹ who found that inulin is hydrolyzed partially by the hydrochloric acid of the stomach and that the feces of individuals fed a varied diet contains an inulin-splitting substance.

Inulin is a gamma-glucoside-fructose-ester. Krantz and Carr¹⁰ in their

*Received for publication, April 23, 1931

physicochemical investigations of the carbohydrate contained in *Arctium lappa*, have published evidence which seems to indicate that this substance has not the same degree of molecular complexity as inulin, as it occurs in the dahlia and in the tubers of Jerusalem artichoke. On the other hand, it corresponds to the inulinin isolated by Tanret,¹¹ having a molecular weight of about 1500 rather than about 5000 which is the assigned value of the molecular weight of inulin. One gram of inulin was shown by Gottschalk¹² to have a caloric value of 4.19 calories. He suggested that the usefulness of inulin in diabetes of the mild type is due to the fact that its hydrolytic product, levulose, has an insulin-enticing action. Levulose is a more labile monosaccharide than is glucose, and it may have the capacity to call forth to a greater degree than glucose, the reserve insulin of the islets of the pancreas.

Solarino¹³ showed that if dogs were fed 5 grams of inulin simultaneously or shortly before or after the ingestion of 25 grams of glucose, the hyperglycemia that resulted was less than when glucose only was given. Likewise, Ciaccio¹⁴ and Racchuisa showed that inulin lowered the hyperglycemia caused by glucose in dogs. Like Gottschalk they felt that this inhibiting action was dependent upon the action of inulin on the internal secretion of the pancreas.

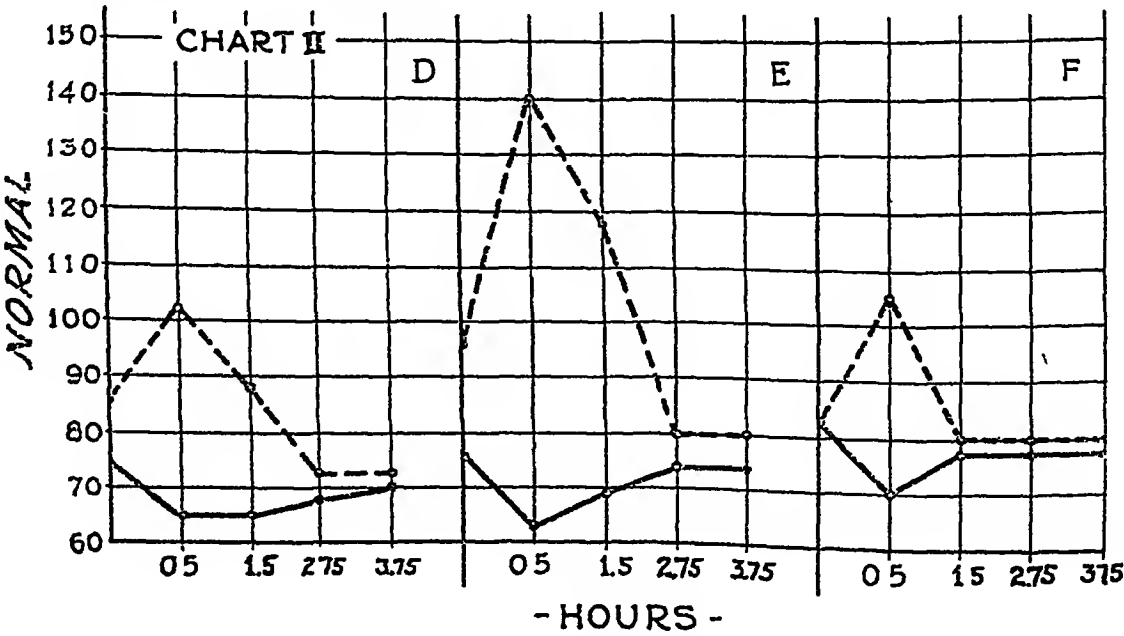
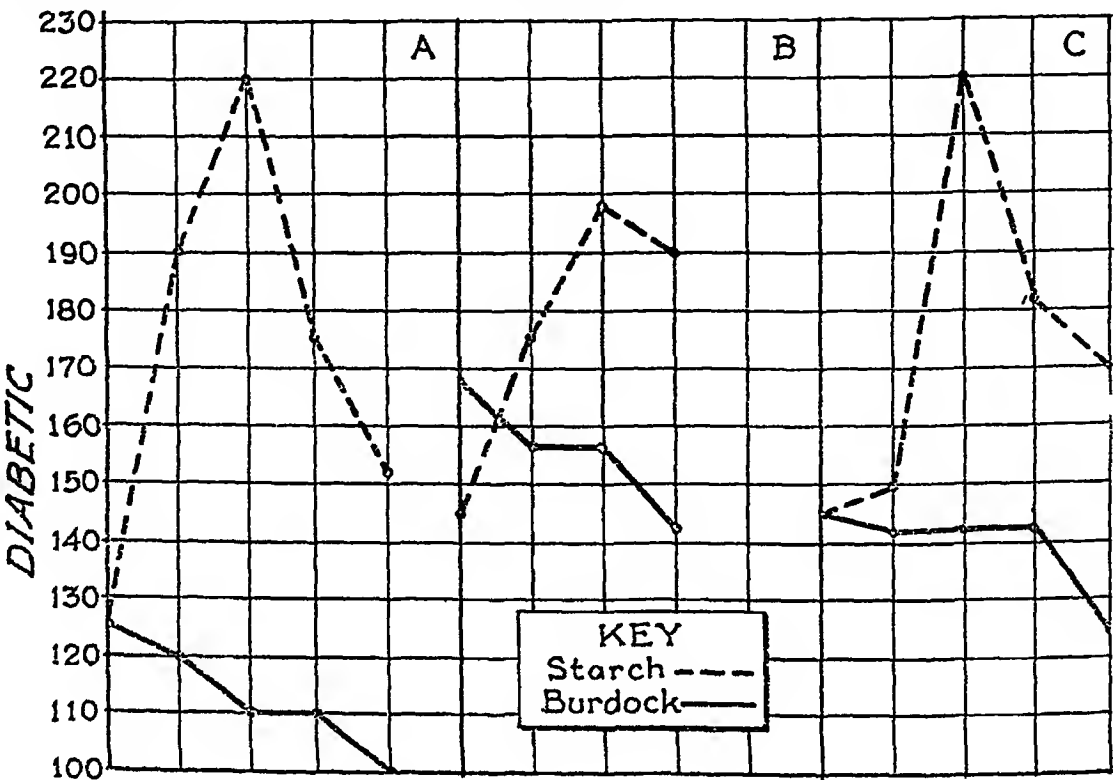
Recently Root and Baker¹⁵ and Carpenter and Root¹⁶ observed a patient in whose diet artichokes furnished the greater portion of the carbohydrate. Although this patient remained sugar-free on this diet, the substitution on

one day of an equivalent amount of carbohydrate in the form of baked potatoes was accompanied by a rise in the blood sugar and the prompt appearance of sugar in the urine. The resumption of Jerusalem artichokes on the next day was accompanied by a lowering of the blood sugar and a disappearance of urinary sugar.

Krantz and Carr^{17,18} have shown experimentally that in white rats powdered burdock root causes an increased storage of glycogen in the liver, and further that in dogs it is anti-ketogenic and has a protein-sparing action. These investigators considered these data to be evidence of the absorption and the utilization of this carbohydrate.

With the foregoing facts in mind the influence of the administration of powdered burdock root upon diabetic patients was observed. The first problem was the production of a food-stuff sufficiently palatable to be substituted easily for other carbohydrates in the diet. The dried root was powdered and extracted with ethereal solvents. This left a powder containing about fifty per cent of carbohydrate hydrolyzable into levulose, a small amount of fat and bitters. The remainder was cellulose. By exposing the powder to low heat, the fat and the bitters were driven off. Later, we found that by re-extracting the powder with an acetone-alcohol mixture, the fat and bitters were more completely removed. This left a powder containing sixty per cent of carbohydrate. A batter was made with 90 grams of the powder, 36 grams of butter, water, salt, saccharin, and a few drops of the fluidextract of ginger. Dividing this

Mg blood sugar per 100 cc CARBOHYDRATE TOLERANCE CURVES
CHART I



MIXED CARBOHYDRATE
TOLERANCE CURVES

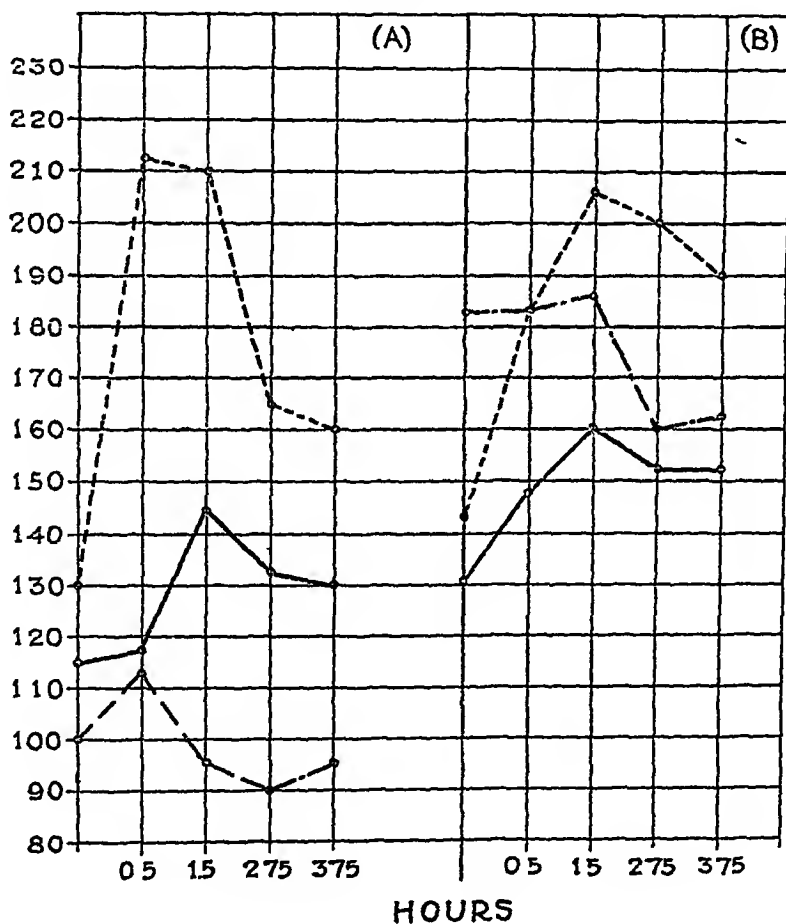
CHART III

~ KEY ~

Starch -----

Burdock - - - -

Combined ———

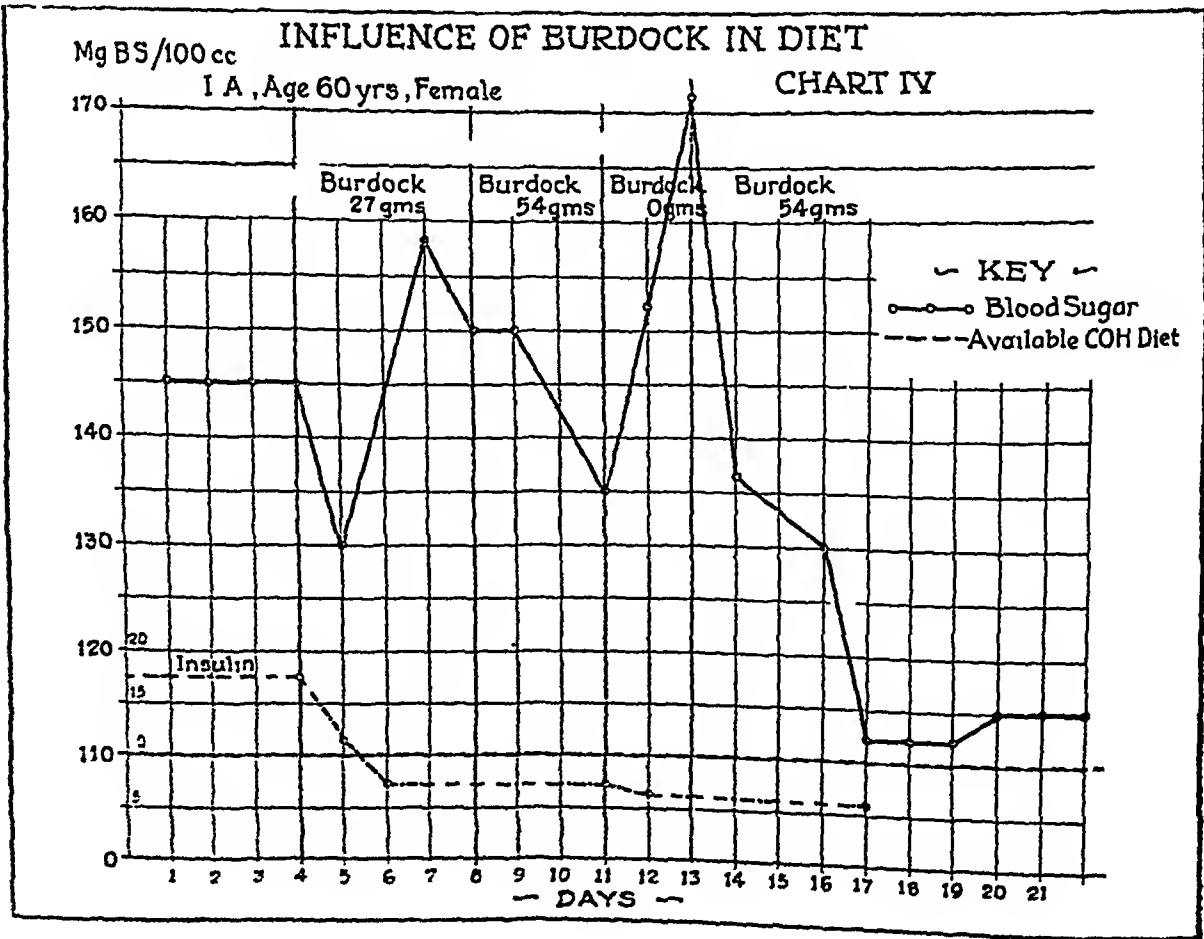
Mg' blood sugar
per 100 cc

into twelve equal parts and baking them as cookies, we obtained a cracker that contained approximately 45 grams of carbohydrate, 3 grams of fat, and 0.2 gram of protein

Three non-diabetic individuals who did not have evidences of disturbance of any of the other glands of internal secretion were studied. In each instance a preliminary determination of the blood sugar was made when the patient had fasted for 12 hours, and then each one was given the equivalent of 100 grams of ordinary carbohydrates in the form of Burdock root. The preparation utilized was a powder containing 80 per cent of carbohydrate, 75 grams of which were suspended in coffee, 28 grams in a flavored gelatin and the remainder in four cookies pre-

pared in the manner described. Determinations of the blood sugar were made one-half hour, one and one-half hours, two and three-quarters hours and three and three-quarters hours after the ingestion of the meal. As a control, on another day, instead of the preparation of burdock root the patients received 100 grams of carbohydrates in the form of oatmeal, canned corn, toasted wheat bread and banana and the blood sugar was estimated at the same intervals of time as in the original experiment. Chart No. II, graphs D, E, and F, show the type of blood sugar curves obtained

It is apparent that when the burdock diet was fed there was a preliminary decrease of blood sugar followed by a gradual rise to just below the



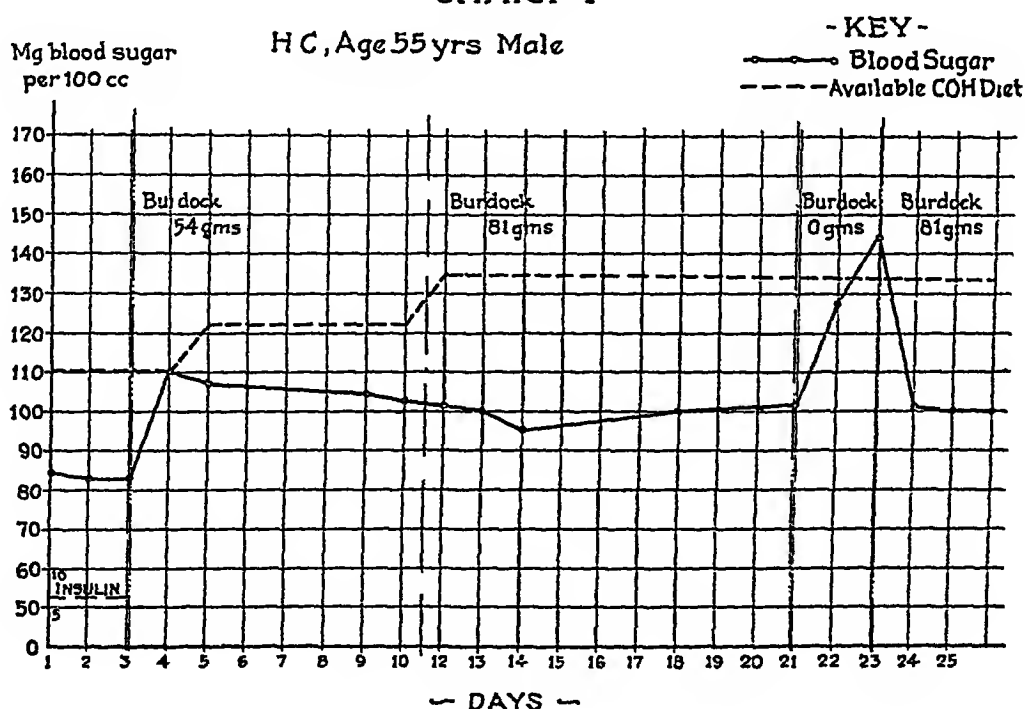
fasting level at the end of three and three-quarters hours. With the meal consisting of carbohydrates other than those in burdock, a curve similar to, but less marked than that of a normal glucose tolerance curve, was obtained.

A similar experiment was carried out with known diabetic patients. To these patients we gave an amount of burdock corresponding to 33 grams of carbohydrate. On another day, under the same experimental conditions, we gave 33 grams of other polysaccharides to these patients. Similar curves were obtained with burdock, and the expected diabetic rise with slow return was obtained with the ordinary polysaccharide meal as evidenced in the following curves (See Chart No. I, graphs A, B and C).

Following the thought that there was an inhibitory factor in burdock on the hyperglycemia of glucose, the following experiment was carried out. Two known diabetics were each given the burdock and non-burdock diets as above described and blood sugars taken at the same intervals. On a third day fasting-blood sugars were taken, the burdock meal was given and followed immediately by a non-burdock meal—33 grams of each. Blood sugars were again taken at the same intervals following the ingestion of the second meal. The curves obtained indicate that there is an inhibitory effect of burdock on the hyperglycemia of glucose (See Chart No. III).

The validity of theory of Gottschalk¹² that the ketone group of lev-

INFLUENCE OF BURDOCK IN DIET
CHART V



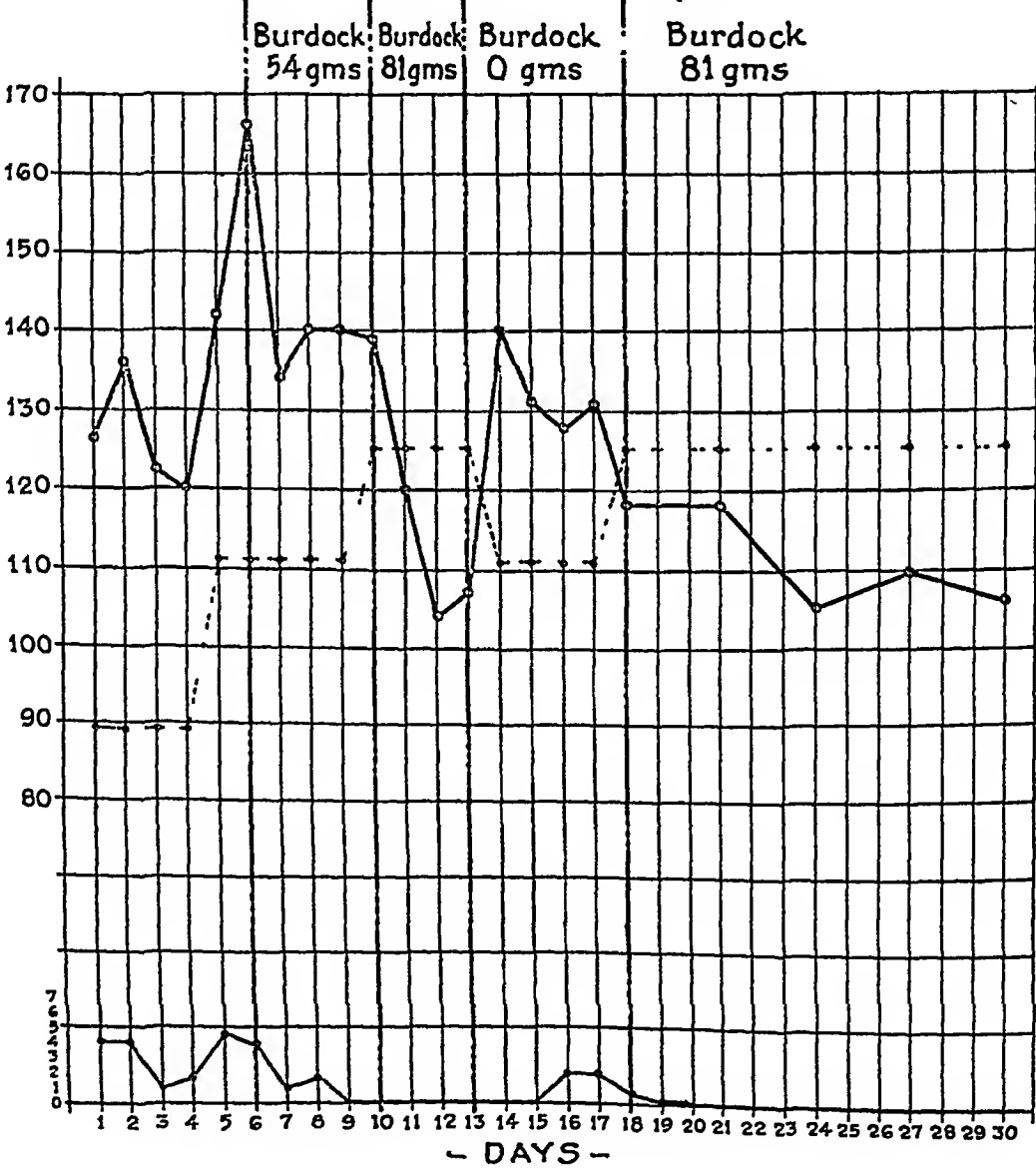
INFLUENCE OF BURDOCK IN DIET

CHART VI.

A S, Age 13 yrs Male

KEY

- Blood Sugar in Mgms per 100 cc
- Available COH in Diet
- Gms of Sugar spilt in Urine in 24 hrs



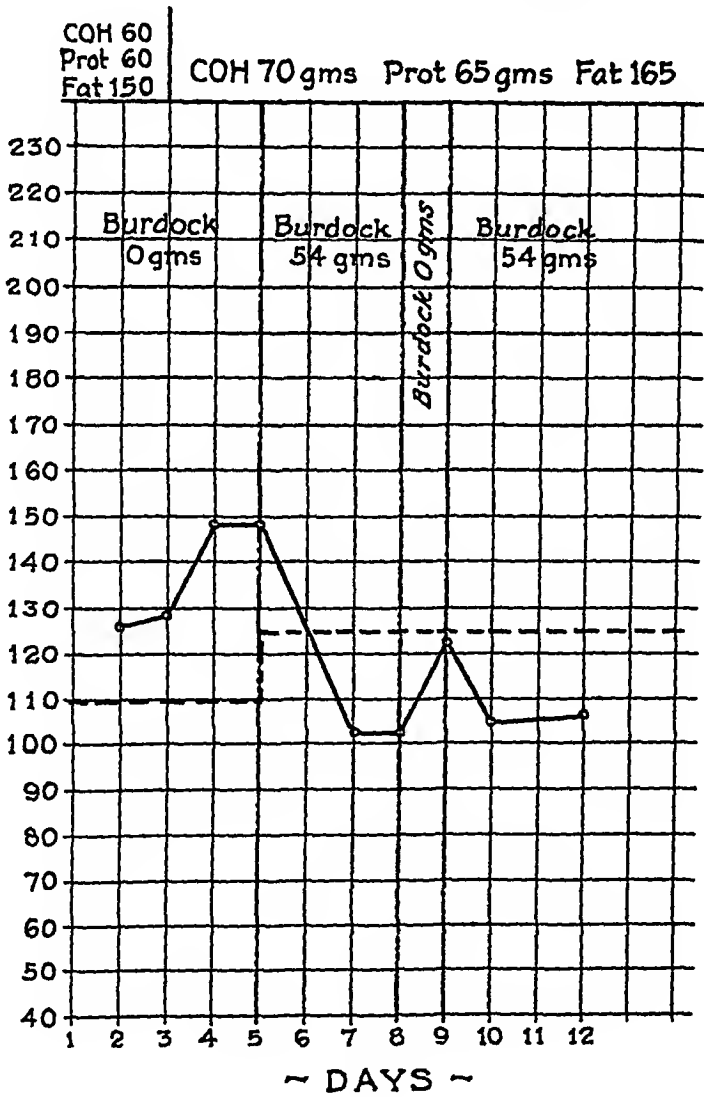
INFLUENCE OF BURDOCK IN DIET CHART VII

H M, Age 46 yrs Male

~ KEY ~

○ — ○ Blood Sugar, Mg per 100cc

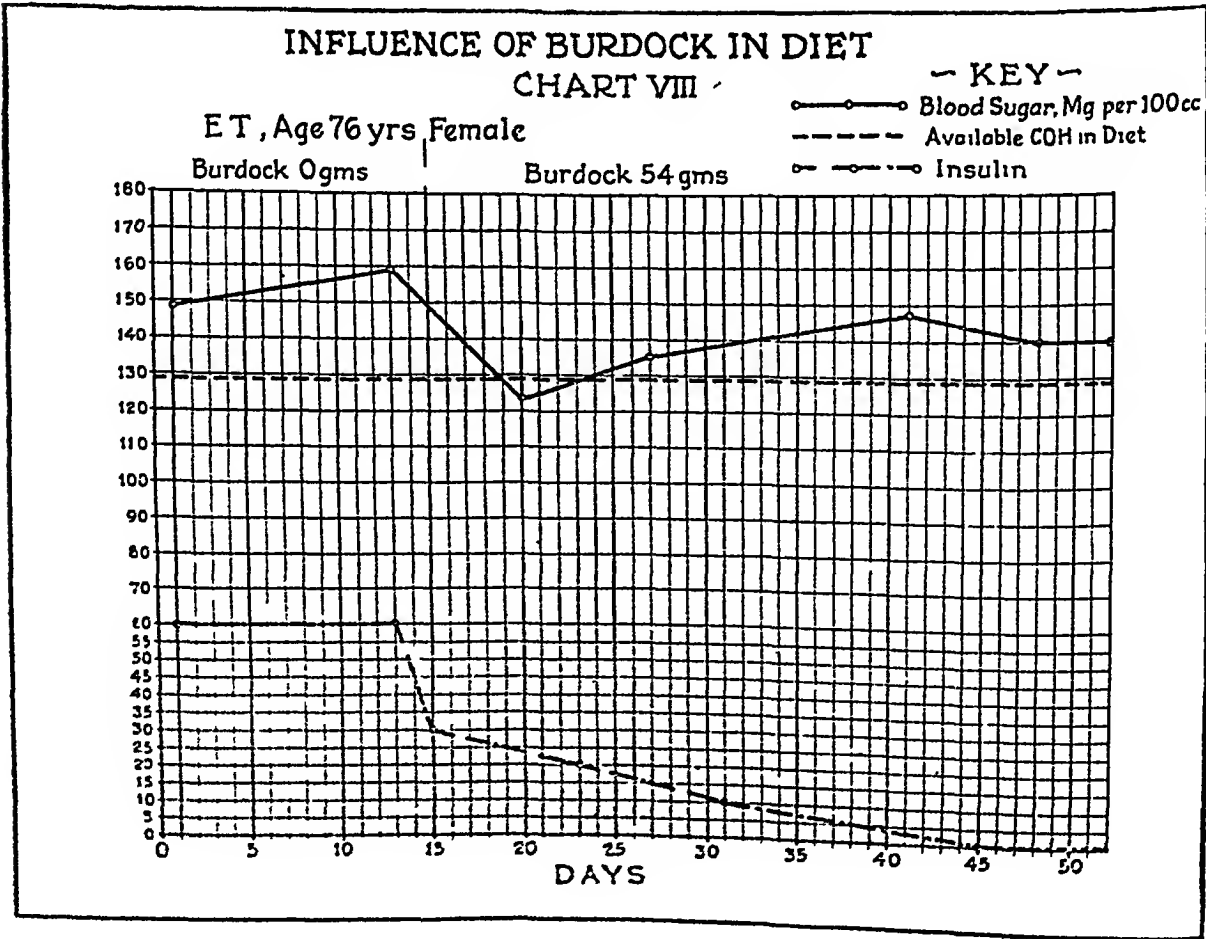
----- Available COH in Diet



ulose is capable of calling forth to a greater degree than glucose, the reserve insulin of the islets, seems to be substantiated by the foregoing results. On the other hand, however, the presence of levulose may hasten the polymerization of the blood glucose into glycogen and in this manner lower the blood sugar level.

Following this work, we began the use of burdock root in the form of crackers as above described as a substitution for the carbohydrates in the diets of several diabetic patients. In accompanying charts IV, V, VI, VII, VIII and IX we have plotted the course of several diabetic patients receiving burdock therapy. In these cases the dosage of insulin was decreased as burdock was administered.

When the blood sugar approached normal the burdock was replaced by other polysaccharides. Immediately there was a marked rise in the blood sugar which returned at once to its former level on replacing the burdock in the diet. This we found to happen in each instance where the foregoing procedure was carried out. In all cases while burdock was being administered there was no glucosuria. However, upon removing the burdock from the diet of diabetic patients and replacing it by other polysaccharides (Uneda biscuits) glucose appeared in the urine. Stool examinations on patients receiving burdock for three successive days showed no copper-reagent-reducing substances after hydrolysis with dilute hydrochloric acid.



INFLUENCE OF BURDOCK IN DIET

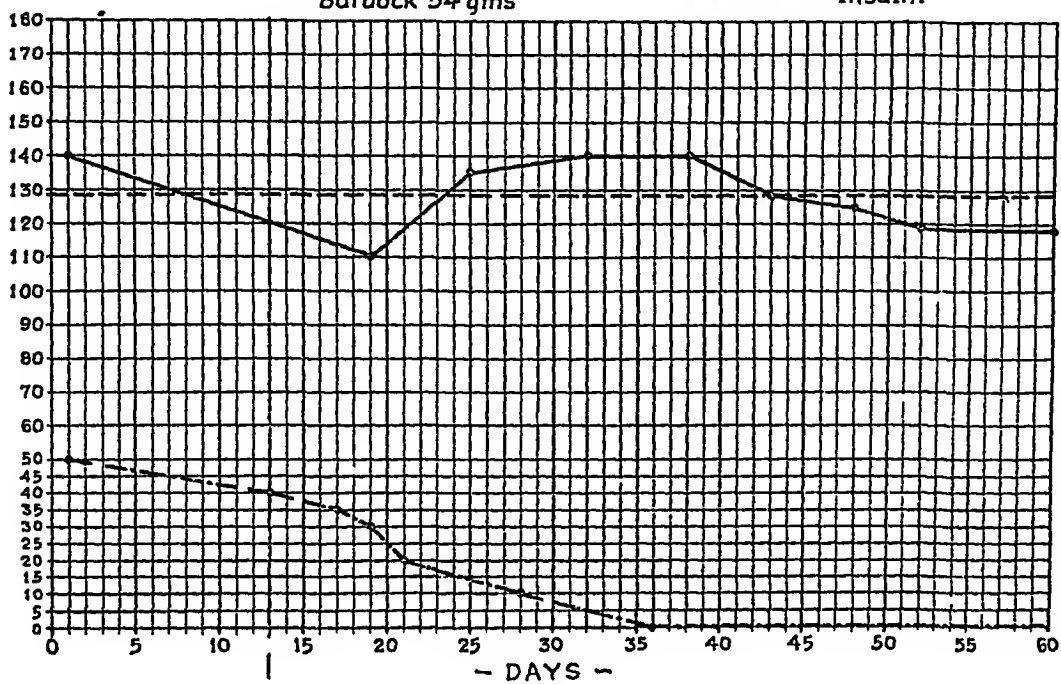
CHART IX

B C, Age 49 yrs Female

Burdock 54 gms

— KEY —

- Blood Sugar, Mg per 100 cc
 - - - Available COH in Diet
 —○— Insulin



SUMMARY

- The carbohydrate in burdock root was absorbed and utilized by certain patients with diabetes mellitus
- In the cases reported burdock root seems to exhibit an inhibitory action on the hyperglycemia caused by the common polysaccharides.
- Powdered burdock root may be easily administered to patients in the form of palatable crackers
- Mild diabetic patients may be kept at normal blood sugar levels and aglucosuric by the administration in their diets of crackers made from powdered burdock root.

REFERENCES

- ¹ SOWERLY Useful plants of Great Britain
- ² NITOBÉ, INAZO Am Jr of Pharm, 1897, lxxii, 416
- ³ ALLEN, F M. Nelson's Loose Leaf System of Med, Vol 3, page 57
- ⁴ CULBRETH, D M R Manual of Materia Medica and Pharmacology, p 615 Lea and Febiger, Philadelphia
- ⁵ BOUCHARDAT, A De le glucosurie ou diabetic sucre, 1875, p 154, Paris
- ⁶ JOHANSON, J E Skand Arch Physiol, 1904, xvi, 264
- ⁷ STRAUS, H Berl klin Wchnschr, 1912, 1213
- ⁸ TANAKA, H Biochem Ztschr, 1911, xxxvii, 249
- ⁹ OKEY, RUTH Jr Biol Chem., 1919, xxxiv, 149
- ¹⁰ KRANTZ, J C, JR., and CARR, C J. Jr. Phys Chem, 1931, xxxv, 756

- ¹¹TANRET, C. Jr. Pharm. Chem, 1893, xxvii, 449 and Compt. Rend., 1893, cxvi, 1143
- ¹²GOTTSCHALK, A. · Ergebn der inn Med und Kinderheilk, 1929, xxxvi, 82
- ¹³SOLARINO, G Arch. di sc biol, 1929, xiii, 31-38
- ¹⁴CIACCIO and RACCHUISA Bollet della Soc Ital di Sperim, 1927, 11, N. 4
- ¹⁵ROOT and BAKER Arch Int. Med., 1925, xxxvi, 126.
- ¹⁶CARPENTER and ROOT Arch. Int Med, 1928, xlii, 64
- ¹⁷KRANTZ, J. C, JR., and CARR, C J. Jr Pharm and Exper Therap, 1931, xli, 83.
- ¹⁸KRANTZ, J C, JR, and CARR, C. J Jr. Pharm and Exper. Therap, in press

Diabetes in the Negro Race*†

By EUGENE J LEOPOLD, M D, *Baltimore, Md*

IT was not so many years ago that diabetes mellitus was considered a rare disease in the colored race. In fact, it is rather common today to hear usually well informed physicians express this belief. This is not altogether surprising since the literature on the subject is indeed meager. It is hoped that such facts as I am able to present will stimulate further study of the subject.

Osler's "Principles and Practice of Medicine" until about ten years ago said diabetes mellitus was rare among negroes. I I Lemann of New Orleans was the first to call to our attention statistics which disproved this statement. In 1911¹ he published studies based upon 61,298 admissions to the Charity Hospital which showed that negroes furnished 40 per cent of the admissions to the hospital and 30 per cent of the diabetic admissions.

The incidence rate was 0.47 per cent against a white rate of 0.072 per cent. In later studies² based on 148,671 admissions during the years 1921-1927 the incidence rates had risen and were 0.34 per cent for negroes as compared with 0.23 per cent for white admis-

sions—higher for the negroes than for the white.

More recently Bowcock reported from Atlanta, Georgia, on the experience of the Grady Hospital and the Gray Clinic with diabetes mellitus in the negro. He³ found among 26,858 admissions to the colored hospital between 1921 and 1928, 112 patients with diabetes, giving an incidence of 0.42 per cent of the admissions.

Table I gives some facts concerning diabetic deaths in Baltimore⁴ for the years 1928 to 1930 inclusive. It shows that negroes formed about 18 per cent of the population of the city and had a considerably higher death rate per hundred thousand inhabitants as compared to the white population, 20.8 and 13.2 respectively. Considering the deaths from diabetes, we find 18 per cent of the population showing a rate of 18.31 diabetic deaths per hundred thousand inhabitants. The remaining 82 per cent white population had a rate of 28.66 per hundred thousand inhabitants. Roughly, for every ten deaths of diabetes per hundred thousand inhabitants among whites, 6.4 negroes died of the disease. One can therefore, no longer consider the disease as a rarity among the negroes of Baltimore. From another viewpoint the same fact becomes evident, during the past three years, ending January 1, 1931, 646 new cases of diabetes mel-

*From the Johns Hopkins Hospital Out Patient Department Diabetic Clinic.

†Presented before The American College of Physicians, Section E, Baltimore, Maryland, March 26, 1931.

TABLE I

Year	Population			Deaths from All Causes			Rate per 100,000 Inhab		
	Total	White	Negro	Total	White	Negro	Total	White	Negro
1928	792,744	655,827	136,917	11,929	8,965	2,964	151	137	216
1929	799,675	659,438	140,237	11,629	8,747	2,882	146	133	207
1930	806,607	663,050	143,557	11,238	8,422	2,816	139	127	196
Aver	799,675	659,771	140,237	11,578	8,711	2,220	144	132	208

Year	Diabetic Deaths			Rate per 100,000 Inhabitants			Diabetic Deaths in Total Deaths, Per Cent		
	Total	White	Negro	Total	White	Negro	Total	White	Negro
1928	229	202	27	2888	3081	1972	192	225	091
1929	109	166	23	2363	2517	1641	162	190	080
1930	226	199	27	2802	3001	1881	201	236	096
Aver	214	189	25	2684	2866	1831	185	221	089

1930—Population 82% White 18% Negro
 All Deaths 75% White 25% Negro
 Diabetic Deaths 76% White 24% Negro
 Diabetic Deaths 235% White 096% Negro

TABLE II

Year	New Admissions to Dispensary				Diabetic Admissions									
	Male		Female		Male		Female		Total		Incidence Per Cent			
	White	Negro	White	Negro	W	N	W	N	W	N	W	N	Lemmann	Bowcock
1927-28	6,346	2,732	6,081	3,701	56	16	110	42	166	58	133	0.90		
1928-29	5,219	2,056	4,658	2,749	60	14	92	51	152	65	154	1.35		
1929-30	4,653	1,940	4,562	2,776	48	18	91	48	139	66	151	1.45		
Totals	16,218	6,728	15,301	8,226	164	48	293	141	457	189	145*	1.27*	3.4	4.2

Total White, 31,519 Total Negro, 14,954

1.45% of white are diabetic

1.27% of negro are diabetic

*May be low as compared to the figures of Lemann and Bowcock because of limited intake of negro patients

litus were admitted to the Diabetic Clinic of the Out Patient Department of Johns Hopkins Hospital Table II shows that of 46,473 new admissions to the Out Patient Department 14,954 were negro patients, 31.9 per cent of the admissions. Among the 646 new cases of the Diabetic Dispensary, 189 or 28.8 per cent were negroes. These figures are somewhat lower than those given by Lemann, 40 per cent admissions and 30 per cent diabetic, and may be due to smaller proportion of negro population in Baltimore as compared to New Orleans. A study made in 1922 of 252 active cases in our clinic showed negroes to represent 22 per cent of the clinic attendance. The average white and colored incidence for the three years was 1.45 per cent and 1.27 per cent respectively. Considering individual years, white incidence was 1.33 per cent, 1.54 per cent and 1.51 per cent and colored was 0.90 per cent, 1.35 per cent and 1.45 per cent. The close approximation of the colored to white incidence may mean that the negroes have a special liking for our clinic. It is out of line with the white and negro death rates given above which show that about 60 per cent as many negroes died as did white persons per hundred thousand inhabitants. Yet it, too, points to the fact that diabetes is a rather common disease among the negroes of Baltimore.

Diabetic deaths in Baltimore in the last three years show a great preponderance of the disease among females. Table III indicates that averaging the three years, 69.2 per cent of the diabetic deaths were in females. When

TABLE III
Diabetic Deaths in Baltimore

Year	Total Deaths		Per Cent Female		Males		Per Cent Negro		Female		Per Cent Negro		Per Cent of Female Deaths	
	Male	Female			White	Negro			White	Negro			White	Negro
1927	63	133			57	6		1.06	114	19		17.7	57.2	76.0
1928	78	151			71	7		0.99	131	20		16.0	57.2	73.6
1929	54	170			50	4		0.80	116	19		10.2	54.0	80.0
Aver.													56.1	76.5

we differentiate between the white and negro deaths, we find the former comprise 56.1 per cent of all diabetic deaths and the latter 76.5 per cent.

In our series of cases in the Clinic 66.2 per cent were female, 64.1 per cent white females and 74.1 per cent colored females

The percentage of white female deaths, 54.0 to 57.2, agrees closely with Joslin's division of clinical diabetics, 55 per cent female and 45 per cent male in the middle decades of life. It is evident both from the death statistics of Baltimore and from the figures from our clinic that diabetes is more common among colored females than it is among white females

A study has been made of 100 unselected negro cases which were treated at the Clinic during the past year. In this group we find 71 per cent are females and 29 per cent males. All of the sources show that diabetes mellitus is found among negroes in a ratio of 30 to 35 per cent male and 65 to 70 per cent female. These figures are somewhat different from most of the reports on the subject. The earlier reports analyzing the occurrence of diabetes by sex were from foreign clinics and showed a preponderance of male diabetics as high as 77 per cent.⁵ Joslin found in a study of 2,646 cases occurring between 1922 and 1927, a reversal of this male preponderance and noted that 55 per cent were female and 45 per cent male. It would seem that negro females are especially prone to the development of diabetes. Bowcock has pointed out that the usual diet among negroes is especially rich in caloric values, in-

cluding such food stuffs as pork, corn-bread, fat meats, and potatoes. The tendency of the negro to live on these food stuffs produces obesity and to this the elderly female is especially prone. Joslin has pointed out that diabetes has increased in frequency even more rapidly among the older negro females than it has developed among white females of the same age group. This seems to be true in the group we have analyzed.

The study of our 100 cases by the age at which they first came under observation is shown in Table IV.

the time of the first visit to the clinic. Perhaps also the well known uncertainty of the negro as to his age may be a factor. Naturally diabetes has in the majority of instances been in existence for some years previous to the first visit. In justification of our classification, let me call attention to the lack of attention given by the negro to symptoms of the disease and the difficulty experienced frequently in attempting to obtain precise facts for the history.

A patient with a weight of ten pounds in excess of the ideal for sex,

TABLE IV
Age Distribution by Decades of 100 Diabetics

Decade	I	II	III	IV	V	VI	VII	VIII
Male	0	2	2	8	6	7	3	1
Female	0	1	2	8	32	28	4	2
Total	0	3	4	16	32	35	7	3
Per cent of 100 cases	0	3.0	4.0	16.0	32.0	35.0	7.0	3.0
Joslin 1927—White	4.6	7.0	8.8	13.0	24.0	26.3	12.8	2.6
Lemann 1928—Negro	—	—	15.5	26.8	31.0	19.7	—	—

Sixty-seven per cent of our group are found in the fifth and sixth decades as compared with 50.3 per cent in white patients as found by Joslin in 1927, and 50.7 per cent in negro patients found by Lemann in 1928. Since children up to the age of twelve years are treated in the Harriet Lane Home, we have no patients in the clinic under thirteen years of age. We have a smaller percentage of cases in the second and third decades than reported by Joslin and in the third and fourth decades than reported by Lemann. Perhaps this difference may be due to the fact that we have classed our cases according to their ages at

age, and height we have considered as obese. It may not be entirely fair to use white standards of weight for the colored race, but we know of no standards for the negro. On this basis 67 per cent of all the cases were obese, 67.6 per cent of the seventy-one females and 67.0 per cent of all the cases. Bowcock found 92 per cent of the females in his series were obese. Perhaps the negro of the more northern districts shows less obesity than in the South because his dietary habits have been modified. Yet this is not borne out. For in the age group from 40 to 60 years, obesity was present in 86.4 per cent of the cases.

Joslin has emphasized the importance of obesity as a factor in diabetes⁶ In a recent study of 1,000 cases he found 77 per cent were above normal weight It would seem that the middle-aged female negress is even more prone to fatness than is the white of the same period Besides, as Bowcock pointed out, instances of excessive overweight are far more common among the negresses than among the white females.

Again, basing our statements upon the date of the first visit to the clinic, there are in this group of 100 cases, 19 cases known to the clinic for five years or longer The longest known is a female who came to the clinic in 1917, aged 52 years, and was placed on insulin in 1924 There is also a male, aged 41 years when he came to the clinic in 1918, who has done well on diet alone In the group of 19 there are 14 females and 5 males Two were in the fourth decade at the first visit, 6 in the fifth, and 11 were 50 years of age or older Lemann found the longest duration among those of his cases in whom onset was in the fifth decade Insulin is being taken by seven of our cases, two males and five females

It is a well known fact that syphilis is very common among negroes Lemann found⁷ among 68,004 negroes in New Orleans evidence of acquired syphilis in 56 per cent of the cases In our series every case has had the Wassermann test, both by water-bath and ice box methods Twenty (20 per cent) of these tests were positive and one test was doubtful This case was a male who gave a history of having had syphilis some years before

He had taken a series of treatments before he came to the clinic Eight other males were positive and fifteen females The amount of syphilis seen in our clinic is in agreement with the findings of Paullin, Davidson and Wood⁸ among negro patients in Atlanta, 22 per cent among Outpatient Department cases and 20 per cent of the negro hospital admissions

Warthin and Wilson⁹ have emphasized the importance of syphilis as a cause of diabetes mellitus We cannot agree with these authors since practically all of our syphilitic cases have had intensive antisiphilic treatment conjointly with their diabetic therapy.* In no instance have we been able to note any improvement of the diabetes which could not be the result of controlling their hyperglycemia by diet alone or diet and insulin We have had several cases in which blood and spinal Wassermann tests have become negative under treatment without showing any effect upon the diabetic conditions In fact, the latter has progressed as a result of inability to keep diet

Based on clinical observation with only infrequent eye examinations, 54 of the 100 cases gave evidence of hardening of the peripheral arteries beyond that to which they were entitled by age Bowcock noted this complication in 55 per cent of his cases Joslin, with more exact examinations, has found an average of all ages of 80 to 90 per cent.

We have found a systolic blood

*[Note by Editor. Antisiphilic treatment cannot be expected to remove fibrosis or sclerosis already established, or to restore island tissue]

pressure of more than 150 mm in 38 cases in which reading has been noted. This is 40.5 per cent of the cases. This is in rather close agreement with the findings of Bowcock.

The occurrence of gangrene in our series is surprisingly small. It is true that we have adopted for use in the clinic a card of directions for the care of the feet as suggested by Joslin. This does not, however, seem to be a factor in the infrequency with which we have met this serious complication in this series. Three of the four cases of gangrene showed the condition when they came to the clinic. The cases were equally divided between males and females, two each. Three of these resulted in mid-thigh amputation. The fourth suffered the loss of a big toe. Lemann noted the condition in 15 per cent of his hospital admissions which might be due to the fact that this serious complication practically always necessitates hospitalization. Another factor explaining the lower incidence is that the negroes of Baltimore are perhaps on a higher sanitary and hygienic level than those of New Orleans, and do not expose their feet as commonly to the elements which Lemann thinks helps to explain the high incidence of gangrene in his cases.

The ferric chloride test of the urine was positive in 14 per cent of our series, 10 females and 4 males. Four cases were admitted to the hospital in coma and all were rescued by insulin treatment. Lemann had 15 per cent of coma in his series.

Fifteen patients, 15 per cent, showed changes in the optic lens. There were twelve females and three males. Our

youngest case was 26 years old when a cataract was noted in his left eye and, upon his return recently, after being absent from observation for seven years another was found in his other eye. Joslin has noted cataract in about 10 per cent of his cases. Spalding and Curtis¹⁰ found it present in 13 per cent of their cases. Since the opening of the Wilmer Ophthalmological Clinic three years ago we are seeing more cataracts constantly. We had one case of bilateral glaucoma and numerous instances of retinitis and other eye conditions.

Thirty of our 100 cases have had insulin treatment, 22 females and 8 males. Lemann gave 19 of his cases insulin and Bowcock likewise. Joslin has stated recently that two-thirds of his cases are now using insulin. The smaller percentage in our series is due to several factors. We have maintained that no clinic case should have insulin unless it actually needs it. Our usual diets have contained from 60 to 80 grams carbohydrate until recently when we have increased this to 100 grams. Cost is an important factor in a group such as we have under consideration. But it does not seem that the negro has any difficulty in carrying out the systematic insulin treatment when it is necessary. It is surprising how few infections we have seen among negroes who are giving themselves the injections. In many instances they are examples of the most complete co-operation despite a meagerness of learning and lack of education. It has not been unusual in the clinic to find a negro who cannot read or write using insulin over years and keeping diet as carefully as do some

of our model white patients. Just one example is case 52, a female, aged 52, known to us since 1917, adjusted to insulin in 1924. She has taken her insulin constantly since then and has effected a 40 per cent reduction in dosage. She has never shown sugar since 1924.

All of these cases were adjusted to insulin in the hospital. We do not attempt to start a patient on insulin in the Clinic, but always give them a period of hospital study before starting injections.

Since this study is one of active cases seen during the past year, we have no deaths to report.

Economic problems occur more frequently among negro patients of an Out Patient Department than among the white cases. These are, in many cases, surmounted by efficient Social Service work. These problems concern the actual providing of diet and, when necessary, of insulin. Perhaps the greatest hindrance among the females is in their occupation as cooks. While the best of colored, as of white, cooks need not taste their cooking to be sure of its proper preparation, many cooks are not so good and must sample the food they prepare.

SUMMARY

- 1 Diabetes mellitus is not an uncommon disease among negroes.
- 2 The death rate of diabetes mellitus in Baltimore in 1930 was 28.02 for white persons and 30.01 for negroes per hundred thousand inhabitants. White deaths from diabetes were 2.36 per cent of all deaths and negro deaths were 0.96 per cent.
- 3 Among the new admissions to the Out Patient Department of Johns Hopkins Hospital negroes formed 31.9 per cent, and 28.8 per cent of the new admissions to the Diabetic Clinic.
- 4 Diabetes in the negro is even more common among females than in the white race.
- 5 A study of 100 cases of diabetes in the negro reveals:
 - Sex: females were about three and one-half times as common as males.
 - Age: 67 per cent of the cases were between the ages 40 and 59 years.
 - Obesity: played the major factor in etiology; 86 per cent of the older females were obese.
 - Duration: in 19 per cent of the group, the patients had been known to the clinic more than five years.
 - Syphilis: does not play an etiological factor in the cause or progress of diabetes.
 - Arteriosclerosis and hypertension were about as common as in non-diabetics of the same age.
 - Gangrene: was seen only four times in the 100 cases.
 - Acidosis: occurred in 14 per cent of the cases.
 - Cataracts: occurred in 15 per cent of the cases.
 - Insulin: was used in 30 per cent of the cases.
- 6 Diabetes in negroes is not different in any way from the disease as found among white people.

REFERENCES

- ¹LEMANN, I I Diabetes mellitus among the negroes, New Orleans Med and Surg Jr, 1911, lxiii, 461-467.
- ²LEMANN, I I Diabetic gangrene in the south, Jr Am Med Assoc, 1927, lxxxix, 659-662
- ³BOWCOCK, H M Diabetes mellitus in the negro race a study of one hundred consecutive cases, South Med Jr, 1928, xxi, 994-999
- ⁴Personal communication from the Health Dept of City of Baltimore, Md
- ⁵GRUBE, quoted from JOSLIN, J E The treatment of diabetes, 1928, 140
- ⁶JOSLIN, J E The treatment of diabetes, 1928, Lea and Febiger, Philadelphia, 159
- ⁷LEMANN, I I Diabetes mellitus, syphilis, and the negro, Am. Jr Med Sc, 1921, clxi, 226-230
- ⁸PAULLIN, J E, DAVISON, H M, and WOOD, R H Incidence of syphilitic infection among negroes in the South, its influence in the causation of disability, and methods which are being used to combat this infection, Boston Med and Surg Jr, 1927, cxvii, 345-350
- ⁹WARTHIN, A S, and WILSON, U F The coincidence of latent syphilis and diabetes, Am Jr Med Sc, 1916, cli, 157-164
- ¹⁰SPALDING, F M, and CURTIS, W S : Retinitis and other changes in the eyes of diabetics, Boston Med and Surg Jr, 1927, cxvii, 165-176

Syphilitic Aortitis in Retrospect*†

By WILLIAM S. MIDDLETON, M.D., F.A.C.P., *Madison, Wisconsin*

THE bedside-necropsy correlation of disease was in a considerable measure responsible for the dawn of modern clinical medicine in the late eighteenth and the early nineteenth centuries. In a majority of instances such studies can admittedly reveal only the irretrievable end products of disease; yet from such determinations it has not infrequently been possible to explain the clinical manifestations of a given entity and to discern its consecutive steps to the fatal termination. In more recent years other allied sciences have lent their impetus to the advance of clinical medicine, but the clinico-pathologic orientation still constitutes one of the most fruitful sources of the maintained growth in medicine.

Visceral syphilis has afforded an ideal field for such correlated studies, and in this direction syphilitic aortitis has received particular attention from Scott,^{1,2,3,4,5} Saphir,^{3,4} Martland⁶ and others. In the conviction that further profit must be forthcoming from similar studies, the records of the Wisconsin General Hospital have been reviewed over a period of four years. During this time twenty-one patients have succumbed to syphilitic aortitis.

Since the pathologic diagnosis has served as the ultimate criterion for the inclusion of each case in the present series, the accustomed order of affairs has been reversed and the pathologic background will be considered before the clinical analysis.

Accordingly the pertinent gross cardio-vascular findings in a typical subject (case 18) are abstracted from the report of the Department of Pathology, University of Wisconsin:

The cardiac apex lies under the seventh rib, 13 cm. to the left of the midline. In situ the heart is twice as large as the subject's clenched fist. The pericardium is smooth but slightly edematous. The pericardial cavity contains 100 cc. of clear yellowish-brown fluid. The heart weighs 623 grams. The right heart is dilated. The apex is made up of the hypertrophied left ventricle. There is a soldier's patch over the anterior aspect of the right ventricle. The several valvular rings measure as follows: tricuspid 14 cm., pulmonic 8 cm., mitral 12 cm. and aortic 10 cm. The left ventricle averages 14 mm. in thickness and the right ventricle, 9 mm. The aortic arch ranges from 7.5 to 8 cm. in circumference. The friability of the myocardium is decreased and it sections with increased resistance. The hydrostatic test proves the aortic valve to be incompetent. The aortic cusps show marked thickening at their bases with calcification. The commissures are widened. The coronary orifices show definite partial occlusion, but the several branches of the two coronary arteries show only occasional small atheromatous plaques. The thoracic aorta shows a saccular dilatation involving the last portion of the de-

*From the Department of Medicine, University of Wisconsin.

†Received for publication February 26, 1931.

scending arch Where the dilated arch impinges upon the vertebral column, there has occurred erosion of the body of the sixth thoracic vertebra on its lateral aspect The entire thoracic aorta is dilated and on section presents many atheromatous plaques, with overlying ulceration in some instances The aneurysmal sac is occupied by a dense laminated organized thrombus, which has somewhat shrunk from the wall of the same on one side and on the other aspect presents a smooth surface medially or to what was the restored blood channel Below the diaphragm the atheromatous changes in the aorta are distinctly less marked

Dr C H Bunting has kindly supplied the histologic description of the heart and the aorta

The myocardium shows hypertrophy with arteriosclerotic changes in the coronary branches There are diffuse patchy areas of myocardial degeneration, which consist of well vascularized, recently organized infarcts of microscopic dimensions Occasionally there are found small cellular masses composed of a few epithelioid and lymphoid cells without characteristic arrangement, but which might be interpreted as degenerated gummata

The sections of the aorta show marked lymphoid infiltration with a few plasma cells about the vasa vasorum in the adventitia and media The intima shows marked fibrous thickening and lymphoid infiltration While these sections of the aorta and others taken through the sinus of Valsalva show unmistakable evidences of syphilis, no gummata can be demonstrated

Turning to the clinical record the following essential notes are gleaned

The subject of this necropsy was an adult, white male 40 years of age who had been a moulder by occupation His chief complaint on admission to the hospital had been shortness of breath, which had been remarked seven weeks previously, coincident with an acute upper respiratory infection A cough which had appeared at the onset had been definitely aggravated by exertion and over-heating A week after the onset a sore aching feeling had appeared in the precordium and this sensation

had persisted up to the time of admission, as had the dyspnea In addition there had occurred a pain in the left side of the back about a year before the onset of the present trouble This pain had grown so severe that at the time of entrance the patient could not lie on the left side Sleeplessness had ensued and added to this the periodic experience of a sudden awakening at night with a profound inability to get his breath had been noted A sense of suffocation with a struggle to get air had been the patient's analysis of these episodes

The inventory by systems had failed to elaborate the above story and the past medical history had revealed no illness of significance The patient had denied the occurrence of venereal disease in any form

The social history had been deemed especially important in the occupational and marital details Born in Poland, the patient had come to America at 21 years of age His work had always been laborious as a farm hand and as a moulder Married first at the age of 27, his first wife had died one year later of an acute abdominal condition, the nature of which had been unknown to the patient There had been no issue from this marriage Three years later he had married a second time This wife remains living and well Three children by this wife are living and well, a fourth had died in infancy of unknown cause

The family history is irrelevant

The pertinent physical findings had been largely circulatory and are herein briefed Orthopnea and cyanosis had been noted The apical impulse had been noted in the left sixth interspace 12.5 cm from the midline Further systolic impulses had been observed in the second and third interspaces A double thrill had been palpated over the second interspaces close to the sternum to either side A supracardiac cap of dullness had been demonstrated The cardiac borders had been noted thus

Right	Interspace	Left
mm		mm
42	2	31
48	3	44
46	4	95
	5	126
	6	148

A loud blowing systolic and a diminuendo diastolic murmur had been audible over the entire precordium. A separate apical systolic murmur had been noted. The transmission as well as the point of maximum intensity of the several murmurs had been rendered difficult of elicitation by reason of their loudness and wide dispersion. The peripheral pulse had been ill-sustained and a well marked Duroziez's sign had been established in the femoral arteries. There had been a pronounced capillary pulse. The blood pressure had registered 160 mm of mercury systolic and 58 mm diastolic. The venous pressure had been 10 cm of water. The other signs of note had been the showers of basal congestive râles and the enlarged liver, palpable 10 cm below the costal margin.

The clinical impression had been syphilitic aortitis with aneurysm of the arch, aortic insufficiency, cardiac hypertrophy and dilatation with relative mitral insufficiency, to which had been added the evidences of decompensation in chronic passive congestion of the lungs and liver.

The laboratory findings bearing directly upon the diagnosis had been

- a—Blood Wassermann reaction +++++
- b—Electrocardiogram showing left ventricular predominance, negative T_1 and slurred R_2
- c—Roentgenologic studies repeatedly demonstrating enormous widening of the cardiac shadow particularly in the left ventricular region, increase in the aortic width with sacculation in the descending arch and erosion of the body of the sixth thoracic vertebra.

The clinical course during the hospital stay had been marked by persistence of nocturnal pain. At times such attacks had been initiated by a substernal pain oppressive in nature and persistent. Occasionally a choking spell had occurred and had been accompanied by great numbers of inspiratory and expiratory wheezes and squeaks throughout the chest. Later dysphagia had become apparent. A positive centrifugal venous pulse had been noted shortly after admission and had favored the conclusion of a tricuspid insufficiency. Several syncopal attacks had marked the further progression

of this course. As a rule bloody frothy expectoration and obvious pulmonary edema had attended such attacks. Throughout the period of hospital observation the backache had constituted the one constant complaint. As a rule there had been no exact localization to the same, but it had always been left-sided and had radiated about the lower left chest, although to a lesser degree there might have occurred some radiation to the right at times. Death had resulted on the seventieth day from progressive circulatory failure.

Accordingly it would appear that every detail of the pathologic picture had been anticipated in this instance by the clinical findings and diagnosis. The nocturnal dyspnea, posterior root pains, dysphagia, and the physical and roentgenologic findings of an aortic dilatation and regurgitation with cardiac enlargement occurring in a man of 40 years could leave little doubt as to the etiologic background. The sequence of events was equally apparent. The positive Wassermann reaction was merely confirmatory. The marital history, as is so frequently the case, gave no directional information. Exception may well be taken to the choice of so full blown a case of syphilitic aortitis as a type; and it is further admitted that the division as utilized by Willius,⁷ syphilitic aortitis, syphilitic aortitis with aortic insufficiency and thoracic aneurysm has obvious advantages. None the less the cases herein considered represent end products and as such the above instance is a distinctive example.

The pathologic and the clinical findings for the entire group (21 cases) have been digested in Table I.

The heart's weight constitutes the first point of pathologic comparison. It was recorded in 17 instances, the re-

TABLE I

SUMMARY OF THE PATHOLOGIC AND THE CLINICAL FINDINGS

HEART				Age	Sex	Occupation	Marital History	Symptoms	CLINICAL COURSE				Associated Syphilis	Death
Wt. (gms.)	Aortic Ring	Coronary Sclerosis	Myocardial Degenerat						Clin	Diagnosis		X ray		
										Wass				
250	0.5 cm	None	None	31	M	Laborer	Single	Mental status precluded determination	0	+++++B +++++SF	—	General paresis	Bronchopneumonia complicating malarial therapy	
371	8 cm	Slight arterio sclerosis	Fibrous	52	M	Laborer	Married — 2 children, 2 miscarriages	Initial lesion 12 years ago	+	O B +++++SF	+	Tabo paresis	Paralytic ileus after malarial therapy	
670	8 cm dilatation beyond ring	Patent, athero sclerosis	Pale, fibrous	53	M	Auto mechanic	Married — 6 children, 3 miscarriages	Progressive dyspnoea, 4 yrs, nocturnal paroxysms for 6 months, precordial oppression	+ Aneurysm	+++++B	+	0	Circulatory, pulmonary thrombosis with infarction	
—	8 cm somewhat dilated	Little athero sclerosis	Few gray patches	57	M	Upholsterer	Single	Entirely neurologic	+	+++++B +++++SF	+	Encephalomyelitis, chorioretinitis, optic atrophy	Cerebral hemorrhage	
158	7.5 cm dilatation distally, calcification at base	Atheromatous plaques & calcification.	Gray patches	58	M	Tailor	Married 31 yrs No pregnancies	Asthmatic paroxysms for 8 yrs, later nocturnal dyspnoea, general anasarca	+ Aneurysm	O B O-SF	+	0	Progressive circulatory failure	
677	7.5 cm	—	—	50	M	Laborer	Married 15 yrs. 1 miscarriage	Dyspnoea for 1 year, hemoptysis, edema of feet & legs, recent orthopnoea, precordial oppression	+	O-B	+	0	Sudden pulmonary edema after progressive failure	
783	7 cm, scarring & puckering at base	Narrowing and extreme sclerosis	Fibrosis	45	M	Clerk	Married 7 yrs No pregnancies	Initial lesion 13 yrs ago Dyspnoea 10 days—paroxysmal nocturnal, precordial pain referred to left arm, relieved by nitrites	+	+ B +++++SF	—	Meningo vascular lues	Sudden death	
750	7.5 cm, few warty vegetations	Patent, athero-sclerosis	Fibrosis	54	M	Clerk	Single	Psychotic	0	+++++B +++++SF	+	Tabo paresis	Melanosarcoma	

TABLE I—(Continued)

Age	Weight	III AP I				Age	Sex	Occupation	Marital History	CLINICAL COURSE				Associated Syphilis	Death
		Aortic Regurg.	Coronary Sclerosis	Aortic Degeneration	Symptoms					Diagnosis					
										Clin	Wiss	X-ray			
9	40	7 cm, pericardial effusion, multiple dilatations above	Slight atherosclerosis	0	55	M	Laborer	Widower, wife died 4 yrs ago Tuberculosis No pregnancies	Cough for two months, hemoptysis daily, increasing hoarseness, aching left shoulder	+	O-B O SF	+	0	Hemorrhage from rupture of aneurysm into left upper lobe	
10	40	9 cm, left ventricle thickened slightly	None	Fibrous, some necrosis	52	F	Housewife (Laborious work)	Widow 17 yrs 4 children, no miscarriages	Dyspnoea to orthopnoea 3 years, choking sensation, substernal oppression, hemoptysis	+	++++B	+	Tabes	Progressive circulatory failure	
11	41	7 cm, cups, high arched and sclerotic, vegetations	Single plaque	Atrophy of fibres	60	F	Housewife	Married 16 yrs 6 children, 1 miscarriage (late)	Early fatigue and dyspnoea for 3 years, cough and palpitation	+	++++B	—	0	Circulatory failure of vegetative endocarditis	
12	40	8 cm, fusion of cusps, calcified base	Potent atherosclerosis	Soft gray fish patches of fibrosis	65	M	Machinist	Married 46 yrs 2 children, then two miscarriages	Gastric crises for ten years	+	O B O SF	—	Tabes	Cerebral deterioration, bronchopneumonia	
13	40	8 cm, few vegetations	Atheromatous plaques	Numerous fibrous areas	66	M	Salesman and sailor	Single	Abdominal distention for 4 months, general anasarca, dyspnoea for 1 week (Initial lesion 40 years ago)	+	++++B	+	Cirrhosis of liver	Ruptured esophageal varix	
14	—	8 cm, involvement of valves	Occasional atheromatous plaques	Occasional irregular gray area	56	M	Printer	Married 21 yrs 2 children, no miscarriages	Primary lesion 25 years ago, recent dyspnoea	+	++++B ++++SF	+	Tabo-paresis	Bronchopneumonia, pyelonephritis	
15	—	Rupture 3 cms above sinuses	—	Fibrosis	55	M	Cigar maker	Married 29 yrs 6 children, no miscarriages	Indefinite dyspnoea and palpitation, mental status confusing	+	O B ++++SF	+	Tabes	Progressive circulatory failure with terminal rupture of aorta, pulmonary thrombosis	

16	560	8 cm, widened & relaxed	Slight atherosclerotic change	Fragmented cells, fibrosis & edema	39	M	Manufacturer	Married?	Initial lesion 15 years ago	+	? + B + + + + + SF	+	General paresis	Circulatory failure complicating malarial therapy
17	Saved with aorta gross specimen	8 cm, dilated, cusps thick, aneurysm of unornament	Extensive atherosclerosis	Fibrosis, fatty degeneration (tigroid)	61	M	Physician	Married at 35 with 2 children, no miscarriages, again at 55 with no pregnancies	Dyspnoea for 8 months, orthopnoea for 2 months, general anasarca 1 month	+	+ + + + + B	+	Tubes	Circulatory failure with terminal bronchopneumonia
18	623	10 cm, extension of aortic involvement	Luebic involvement of orifices, atherosclerotic plaques	Gumma (?), fibrosis	40	M	Farmer, Moulder	Married 14 yrs wife died in 1 yr no pregnancies, remarried 10 yrs 3 children, no miscarriages	Sore aching in precordia for 4 months, severe excruciating pain in back to both sides, nocturnal dyspnoea	+	+ + + + + B	+	0	Progressive circulatory failure, erosion of vertebra by aneurysm
19	787	9.5 cm, widened, cusps intet	Marked atherosclerosis	Hypertrophy, edema and fibrosis	54	M	Cook	Single	Dyspnoea for two years, progressive to orthopnoea, general anasarca	+	0 B	+	0	Progressive circulatory failure, cerebral hemorrhage
20	305	6.5 cm	Slight atherosclerosis	Fibrosis	19	F	Housewife	Widow 2 yrs, Married 19 yrs 1 child, no miscarriages.	Palpitation and dyspnoea, some edema of ankles	0	0 B + + + + + SF	—	General paresis (men vasc lues)	Rapid circulatory failure
21	170	8.5 cm, widened orifice, thick cusps	None	Fibrosis, hypertrophy atrophy & fatty degeneration	34	F	Housewife	Divorced 1 yr after 4 yrs married, no pregnancies	Precordial pain 7 1/2 months, dyspnoea, dependent edema, recent palpitation	+	+ + + + + B	—	0	Infected infarct of lung and bronchopneumonia, rapid circulatory failure

0 Negative or None
— No observation made

maining four figures having been sacrificed when the gross specimens were kept intact for museum purposes. Of these 17 hearts, 13 were from male subjects and averaged 468 3 grams (range, 250 to 787 grams). Only three of the 13 (250, 280 and 290 grams, respectively) weighed within the accepted normal limits. There were four hearts from female subjects weighing 420 7 grams on an average (range 305 to 470 grams). A single heart, 305 grams, from a female subject was possibly within the normal range.

The aortic ring circumference was recorded in 20 instances (16 males and 4 females). The average from the males was 7.9 cm with ranges from 6 5 to 10 cms, whereas the aortic ring in the hearts of female subjects averaged 7 8 cms with a range of 6 5 to 9 cms. Three males and one female showed aortic rings of normal circumference. A casual relationship might be anticipated between the dilatation of the aortic ring and the degree of left ventricular hy-

pertrophy, hence the cardiac weight. By the same token the smaller hearts might be expected in those cases where no dilatation has occurred in the aortic orifice. Therefore, in Table II the extreme weight figures for the two sexes have been taken and the measurements of the respective aortic rings placed in parallel columns.

The lack of close correlation becomes apparent at a glance. In other words there is no direct relationship between the cardiac weight and the size of the aortic orifice. The heart may be grossly hypertrophied without dilatation of the aortic ring. While in general the heavier hearts fall into the group with the wider aortic orifices, enough exceptions are noted to jeopardize any rule. The work of Saphir and Scott,^{3,4} in particular, affords the logical explanation for such exceptions in that regurgitation may readily take place through sagging aortic valves whose bases are the seat of syphilitic invasion without actual dilatation of the rings.

In only one instance (case 18) was

TABLE II
COMPARISON OF HEART WEIGHT AND AORTIC RING CIRCUMFERENCE

Case Number	Heart Weight (Grams)	Aortic Ring (Cm)
Male		
1	250	6 5
12	280	8 5
13	290	8
19	787	9 5
6	677	7 5
3	670	8
Female		
20	305	6 5
10	495	9

there involvement of the coronary orifices in the syphilitic process. Sixteen of 20 subjects (one had no note) showed atherosclerosis of varying degrees in the coronary arteries. Macroscopic or microscopic evidences of myocardial degeneration were noted in 17 cases. This figure is conspicuously high, and when the age distribution is considered, its significance will be even more apparent. In one case only (case 18) could histologic evidence of a syphilitic etiology be deduced from the cellular changes in the myocardium.

No detailed discussion of the findings in the aorta is necessary in this connection. The longitudinal striation of the intima and its distribution in the beginning of the aortic arch are important details known to every clinician. If more widespread, the diaphragm almost invariably marks its lowest extension. The nature of the syphilitic involvement of the aortic ring is somewhat less familiar, but its first description by Tripiér⁸ is

exact and his accompanying cut (figure 1) completes the picture.

Mais ce qui apparait d'une maniere tres evidente dans la plupart des cas (15 fois sur 20), c'est qu'il existe entre les bords d'insertion valvulaire, contigus a l'etat normal, un écartement d'un a plusieurs millimètres que nous n'avons jamais rencontré qu'avec une altération de cette nature et qui nous semble des lors constituer pour elle un caractere pathognomonique.

To the importance of this widening of the commissures between the aortic cusps conclusive observations have been brought by Scott and Saphir,^{1,2,3,4,5} who are responsible for the present day appreciation of this detail. Sight must not be lost of the frequent overshadowing of the gross luetic picture by atherosclerosis of the aorta, and as Warthin⁹ has pointed out "when the picture is that of atherosclerosis no positive exclusion of syphilis can be made without a microscopic examination." Hence it should be borne in mind that when the gross appearance of the aorta with its atheromatous plaques and ulcerations is most



FIG. 1. Widening of the commissures of the aortic valve (from Tripiér)

distinctly atherosclerotic, the necessity for the histologic proof or exclusion of syphilis is even greater than when the appearance is obviously syphilitic. The criteria for a histologic diagnosis of syphilitic aortitis are embodied in the report of case 18 and they have served as the basis for inclusion of all cases in the present series. There is no necessity for reiteration of these details.

Turning to the clinical picture the social history first arrests the attention. There was only one negro in the group. As to age, 18 of the 21 individuals were under 61 years of age and 10 of the group were between 51 and 60 years, inclusive. There were 17 males and 4 females, a ratio of slightly more than 4 to 1. The severity of occupation seemingly bore little relation in predisposition in that 9 individuals followed sedentary work as compared with 12 in laborious trades.

The marital side of the social history was very illuminating. At the time of admission 5 were single, 12 married, 3 widow or widower, 1 divorced. Of the sixteen individuals sometime married, 4 were partners in sterile unions and miscarriages had occurred in 4 other couples. In other words 50 per cent of the married group had procreative disturbances.

The histories afforded but little accurate data relative to the initial lesion. In only four instances was the occurrence of a chancre admitted and the intervals in these cases were widely separated (12, 15, 25 and 40 years respectively). Of greater importance in the present relation was the subjective history of these patients

with syphilitic aortitis. Dyspnea was the outstanding complaint in 14 and it was apparently a rather late manifestation in the majority of instances. Paroxysmal nocturnal dyspnea does not occur early enough nor regularly enough to be of great help in differential diagnosis, but given the manifestation of sudden starting from sleep with a feeling of choking or of inability to breathe, syphilis of the aorta should receive first thought in explanation. Particularly is this the case when the dyspnea is so severe as to lead to fear of death. Pain was a subjective complaint in only four instances. The low incidence of this symptom is not offered as proof of its inconsequence. As a matter of fact true substernal oppression has a real bearing upon the diagnosis, but anginal attacks and posterior root pains must obviously be related to the special parts involved. Interestingly, case 18 was the only subject to show encroachment of the syphilitic process upon the coronary orifices, yet he escaped anginal attacks. It will likewise be noted that precordial oppression may occur in luetic aortitis in the absence of aneurysms (cases 6 and 10).

The diagnosis of syphilitic aortitis is simplified if aneurysmal dilatation has occurred. Pressure phenomena and characteristic physical signs render the nature and location of such a vascular sac quite exact. These circumstances will account for the diagnosis of four aneurysms of the aorta included in this series. Of the remaining 17, a diagnosis of luetic aortitis was made in 14 from the history and the physical signs without recourse to the labora-

tory As has been previously pointed out, these cases were late examples of the process Helpful signs in their recognition included suprasternal impulses, seen or felt, impulses to the right of the sternum in the second interspace, systolic shock by trans-thoracic palpation, displacement of the cardiac apex down and to the left, widening of the cardiac dullness to the left, supracardiac cap of dullness or dullness under the manubrium, peculiar "bottom of the well" quality to the aortic second sound, systolic slurring with a short rough murmur in the second right interspace transmitted slightly to the vessels of the neck, and ultimately to clear-cut auscultatory evidences of aortic insufficiency without a rheumatic or a septicemic background

A word further may be offered in explanation of certain of these signs In palpating for the aortic arch the finger should be placed in the suprasternal notch and then it should be sharply flexed as pressure is made retrosternally The patient is instructed to flex the neck In the normal (unemaciated) subject the arch of the aorta cannot be reached by this manipulation, but in syphilitic involvement with loss of elasticity of the aorta, elongation in the long axis is the first response Hence it is sometimes possible to palpate the arch by this technique before any other sign is demonstrable (Figure 2) Hoover's¹⁰ suggestion of the bimanual trans-thoracic palpation for the thrust of the elongated aorta has been largely overlooked He advised placing the right hand over the right second interspace close to the sternum and the left hand

over the left interscapular space To the palpable impulses which are frequently felt in syphilitic aortitis he applied the terms, systolic shock and diastolic impact These terms are quite descriptive However, this simple aid has frequently been neglected Innumerable qualifying terms have been applied to the aortic second sound in syphilitic aortitis *Bruit de tabouka* is a favorite, but the Algerian drum is not a familiar musical instrument to most physicians The tone has always suggested the quality of sound elicited by dropping a pebble into a well, hence the suggestion of a "bottom of the well" sound The impression gathers with the growing literature on the subject that the profession is seeking a short-cut to the accurate diagnosis of syphilitic aortitis and in the process is neglecting the time-tried and proved methods of physical examination

The laboratory does have a very important and indispensable place in the diagnosis of syphilitic aortitis Of these measures the Wassermann reaction suggests itself as the most available All patients had the Wassermann reaction studied in the blood The spinal fluid was subjected to this test in 12 cases Of the 21 specimens of blood tested there were 13 positive and 8 negative reactions whereas of the 12 spinal fluids there were 9 positive and 3 negatives A number of combinations suggest themselves, but the most helpful considerations lie in those which offer a check upon the negative blood Wassermann reactions In 6 cases with negative blood Wassermanns the spinal fluid was studied and in 3 of these it was

negative and in an equal number, positive. In 2 other instances a low titre in the blood was checked by strongly positive reactions in the spinal fluid. The present series includes a considerable number of individuals with syphilis of the central nervous system, and any evaluation of the relative importance of the Wassermann reactions in the blood and in the cerebrospinal fluid must take this detail into account. Indeed, all of the five cases in which a negative or a faintly positive blood Wassermann was paralleled by a positive spinal fluid, were diagnosed

as various types of central nervous system syphilis. Nevertheless, the check of a negative blood Wassermann reaction by a positive return from the cerebrospinal fluid is sufficiently common to warrant its consideration.

Increasing importance is being placed upon the fluoroscopic study of the heart and great vessels in luetic aortitis. As pointed out by Kurtz and Eyster,¹¹ the elongation and the widening of the aorta together with the pulsation to the right of the sternum and the visibility of the descending aorta in a subject under 50 years of



FIG. 2. Roentgenogram showing the position of the finger in retrosternal palpation. Contrast for the finger-tip has been afforded by barium sulphate in a rubber cot.

age constitute suggestive criteria for the diagnosis of aortitis. Any construction of such data into etiologic background must obviously be presumptive, but in principle and practice such grounds for the diagnosis of aortitis would appear sound, at least until that stage of life when sclerotic changes make their appearance in the vascular bed. Added to the fluoroscopic examination of the aorta itself should be routine orthodiascopy for cardiac size and contour. Of somewhat less general application and value are teleroentgenograms for cardiac size and oblique or lateral views for the retrocardiac space. If the obvious assistance in the diagnosis of aneurysm in four cases be eliminated from the present discussion, there remain 17 patients upon 11 of whom roentgenologic studies were made. In all of these, adequate data were derived from such observations to warrant a conclusion of aortitis. In one instance (case 8) a negative cardiovascular diagnosis from a clinical standpoint was made positive by roentgenologic study. Unfortunately the other two negative clinical diagnoses (cases 1 and 20) were not checked by roentgenologic examinations.

Syphilis of the central nervous system was associated with syphilitic aortitis in 12 cases. This figure is exaggerated in a clinical sense, for only six of this group showed predominant central nervous manifestations. The remaining six cases so classified were diagnosed in part upon neurologic findings of an objective order or by serologic studies on the cerebrospinal fluid. It must be concluded that for this series, at least, the coincidence of

syphilis of the aorta and of the central nervous system was very high. One patient (case 13) had syphilitic cirrhosis of the liver.

The manner of death constitutes the final point of clinical interest. Circulatory failure accounted for 10 of the group. Of these the termination was sudden in three and slowly progressive in seven. The next most common method of exitus was collapse succeeding malarial therapy. The occurrence of three deaths attributable to this cause should give pause to the use of malarial therapy in central nervous system syphilis complicated by syphilitic aortitis. The other directly determining causes of death were scattered: thus cerebral accident, 2, broncho-pneumonia, 2, rupture of aneurysm, 1, rupture of aorta, 1, ruptured esophageal varix, 1, melanosa, 1.

CONCLUSIONS

Bearing in mind that the group of cases above analyzed represents end-results of syphilitic aortitis in the main, certain conclusions seem justifiable.

1. The diagnosis of syphilitic aortitis in the late stage was relatively accurate by physical methods, abetted by an adequate history.

2. Roentgenologic technique may effect an earlier diagnosis but the etiology cannot be so determined.

3. The Wassermann reaction on blood was positive only in 61 per cent of cases, but further assistance is offered in this direction by the higher incidence of a positive reaction in the cerebrospinal fluid. Hence a check

of all negative bloods by spinal fluid study may be worthy of consideration where doubt exists as to the etiology of an established aortitis

4 Most subjects with syphilitic aortitis succumb from circulatory failure. Failing an early recognition and arrest of the syphilitic process, treatment must later resolve itself into an effort to preserve and support

a failing myocardium in which apparently an intercurrent coronary sclérosis of non-syphilitic origin is the determining factor in inducing degenerative changes

5 Malarial therapy imposes a heavy burden upon the myocardium. Accordingly it should be avoided whenever there is evidence of aortitis with aortic valve involvement

REFERENCES

- ¹SCOTT, R. W. Syphilitic aortic insufficiency, *Arch Int Med*, 1924, xxxiv, 645
- ²SCOTT, R. W. Latent syphilis as a cause of heart disease, *Ann Clin Med*, 1927, v, 1028
- ³SAPHIR, O. and SCOTT, R. W. The involvement of the aortic valve in syphilitic aortitis, *Am Jr Path*, 1927, iii, 527
- ⁴SAPHIR, O. and SCOTT, R. W. Observations on 107 cases of syphilitic aortitis, with special reference to the aortic valve area, the myocardium and branches of the aorta, *Am Heart Jr*, 1930, vi, 56
- ⁵SCOTT, R. W. Symptoms and clinical course of syphilitic aortic insufficiency, *Am Heart Jr*, 1930, vi, 86
- ⁶MARTLAND, H. S. Syphilis of the aorta and heart, *Am Heart Jr*, 1930, vi, 1
- ⁷WILLIUS, F. A. A study of the course of syphilitic cardiovascular disease, *Am Heart Jr*, 1930, vi, 113
- ⁸TRIPIER, R. *Etudes Anatomico-Cliniques, Coeur-Vaisseaux-Poumons*, 1909, Paris
- ⁹WARTHIN, A. S. The new pathology of syphilis. The Harvey Lecture, 1917
- ¹⁰HOOVER, C. F. Aortitis syphilitica, *Jr Am Med Assoc*, 1920, lxxiv, 226
- ¹¹KURTZ, C. M. and EYSTER, J. A. E. Fluoroscopic studies of the heart and aorta in acquired and congenital syphilis, *Am Heart Jr*, 1930, vi, 67

Bronchomoniliasis: A Clinical and Pathological Study with Report of Illustrative Cases*

By OTIS S. WARR, M.D., F.A.C.P., *Memphis, Tennessee*

GENERAL HISTORY

THE history of the higher vegetative organisms began with the work of Hook¹ in the seventeenth century. Saccardo,¹ in 1886, compiled and summarized the information gained up to that time regarding these organisms as pathogenic agents. The revolution in medicine which followed the great discoveries of Pasteur and Koch caused bacteriology to eclipse mycology and only within the last twenty-five years has interest been revived in this important study, due chiefly to Sabouraud, Castellani and Pinoy, and their associates. Castellani has isolated many varieties of monilia and has described the disease entity known as "bronchomoniliasis".

Bronchomoniliasis is a disease of the respiratory organs caused by a fungus of the Genus *Monilia*. From Ceylon, in 1905, Castellani^{1,2} published the first description of this affection and since then cases have been recorded in all climates. From Seattle to Siam, from Baltimore to Buenos Aires come case reports. The only continent

from which reports are lacking is Australasia. In 1915, Boggs and Pincoffs³ reported from Baltimore the first case of pulmonary moniliasis in the United States and since then the disease has been observed from the Great Lakes to the Gulf of Mexico and from the Atlantic to the Pacific, although in the intervening fifteen years only eleven other reports⁴ have appeared in our medical literature.

In tropical and subtropical countries bronchomoniliasis is much more common than in the temperate zone, but, masking under the guise of tuberculosis, it occurs in all climates, no doubt, with much greater frequency than is generally recognized. Realization of the cosmopolitan nature of monilia infection, indistinguishable as it is clinically from tuberculosis, will lead to growing appreciation in all parts of the world of the value of prompt recognition of this pathological entity, for, in its mild form, this disease readily responds to treatment with iodides but, if neglected or treated as pulmonary tuberculosis, it usually ends fatally.

PATHOGENICITY

Since at present the definite biological relationships between the yeast

*From the Polyclinic and the Department of Medicine, University of Tennessee College of Medicine.

fungi are not settled and fixed grouping for the pathogenic forms is as yet undetermined, some eminent mycologists in this country prefer to concur in the custom, practised abroad, of calling all organisms which produce yeast-like forms in abundance and propagate chiefly by budding, 'blastomycetes' and the diseases produced by them 'blastomycoses', using the terms simply in the generic sense. This terminology is confusing and presents a difficulty to the reviewer, for in the United States the blastomycete is generally regarded as a genus as separate and distinct as the Genus *Monilia* or the Genus *Aspergillus*, and in common usage these terms have only a specific meaning.

The Genus *Monilia*, generally regarded as belonging to the 'fungi imperfecti' or hyphomycetes, is widely distributed in the tropical and temperate zones, and is present in the air, especially of the tropics. It lives in nature in the saprophytic state, thriving on decayed wood, dead leaves, and vegetable debris of all kinds. It may attack any organ or system of the body. Castellani's⁶ first investigations were instigated by the constant finding of monilia, in large amounts and without the concomitant presence of tubercle bacilli, in the sputum of persons suffering from a disease entity simulating pulmonary tuberculosis. These persons were employed in tea factories in Ceylon. In the tea leaves and in the tea dust monilia was also found. This initial finding led to studies which have definitely established a large number of species of the Genus *Monilia* as capable of being the sole causative organism in

bronchopulmonary disease. The many varieties are differentiated chiefly by their biological characteristics, especially fermentation of sugars. The types most frequently found in bronchomoniliasis are *Monilia tropicalis* Castellani, *Monilia pinoi* Castellani, *Monilia metalondmensis* Castellani, and *Monilia krusei* Castellani.

Castellani⁶ found that moniliae with the same biochemical properties may differ enormously in their pathogenicity for man and laboratory animals. Species pathogenic to man may be non-virulent to the usual laboratory animals. The vegetative body or thallus of these organisms appears, in its parasitic stage, as a mass of mycelial threads or free-budding forms in the tissues which it invades. *Monilia* fungi live saprophytically in the human mouth. Parasitically, they attack chiefly the skin and mucous membrane, more rarely the nervous tissue. Bronchopulmonary disease is the most frequent manifestation of monilia invasion. These fungi are not omnipresent but occur in most sputa, and when they appear in large numbers bronchomoniliasis is usually indicated.

Seemingly, the pathogenicity of these organisms in any given case depends largely upon the resistance of the host. In numerous cases a preceding bronchitis, influenza, or pneumonia is mentioned, and in Busse's case, cited by Procházka,⁷ pregnancy and childbirth were apparently primary conditioning factors. Procházka believes that most fungi have only a facultative pathogenicity and that a weakened condition of the host's organism (human or animal) may provide the soil

necessary for the development of full pathogenicity. He suggests that sugar-containing media, such as the sugar beet, may increase the pathogenicity of these fungi. From the consideration that monilia grows best in a medium which contains sugar, Balog and Grossi⁸ believe that it would more readily penetrate a diabetic terrain and they give insulin in consequence. From the analogy with thrush, of which monilia is the most common causative agent, Kotkis, Wachowiak and Fleisher⁹ think it reasonable to interpret bronchopulmonary moniliasis as a condition in which a primary irritating factor, bacterial, toxic or mechanical, initiates changes which permit the fungi to gain foothold, and, once established, to become the essential element in maintaining the irritation.

ETIOLOGIC FACTORS

Most of the cases reported have been in adults, a few suggesting that the infection was contracted in childhood and, after a brief period of activity, lay more or less dormant until middle age. The mode of infection is a matter of conjecture. Undoubtedly, the fungus exists saprophytically in the mouth and may under favorable conditions become pathogenic. Farah¹⁰ and Iacono¹ state that it may be transmitted from man to man. It may be picked up from vegetation, as in the case of the tea factory workers in Ceylon. Balog and Grossi¹¹ believe that the most frequent carriers of the organism in Egypt are dried fruit and straw, and Mautner¹² calls attention to the frequency of the disease among those having close contact with pigeons and other birds, suggesting their food

as a possible source of infection. Since the fungus is prevalent in the air, it no doubt frequently enters the lungs by inhalation. In Ceylon it was found in the nasal cavities of tea-tasters who snuff up tea as well as taste infusions, and Castellani and Chalmers⁵ found that guinea pigs into whose nostrils tea dust was insufflated daily for months developed a broncho-alveolar moniliasis. Haberfield, cited by de Almeida and dos Santos,¹³ thought that the organism entered by inhalation, and later, writing with Lordy, suggested the tonsils as a portal of entry. De Almeida and dos Santos¹³ believe that the organism could travel by the blood stream as well as by the lymph stream.

There are those who agree with Galbreath and Weiss² that at present there is no agreement as to what constitutes the Genus *Monilia* and as to whether it has a primary or a secondary rôle in the etiology of nontuberculous chronic bronchitis. Yet Castellani¹ has grouped the affections due to monilia as follows: (1) Tonsillitis (tonsillo-moniliasis), (2) Bronchitis (broncho-moniliasis), (3) Conjunctivitis (ocular moniliasis), (4) Enteritis (entero-moniliasis), (5) Otitis (oto-moniliasis), (6) Urethritis (urethral moniliasis), (7) Dermatitis (cutaneous and mucous moniliasis). Iacono¹ adds that in certain brain abscesses the cause has been found to be a monilia. Certainly from a nosological standpoint as Farah¹⁰ suggests, every case of bronchitis, especially every one of long standing should be well studied and cultures from the expectoration should be obtained.

SYMPTOMS

Primary broncho-moniliasis appears in three forms, i e, (a) mild, (b) intermediate, and (c) grave. In the mild type the general condition of the patient is good and there is no fever. There is a slight cough with mucopurulent expectoration, often scanty and usually not containing blood. Physical examination of the chest is negative or reveals only a few râles. The intermediate type is characterized by a slight bronchial catarrh and slight fever which is of long duration. The cough, more or less severe, is paroxysmal, occurring morning and night. There may be some degree of dyspnea. In the grave form, the symptoms, the entire clinical picture, and frequently the roentgen picture, closely resemble pulmonary tuberculosis both as to local and general findings. There is the same hectic fever, the gradual and progressive loss of weight, night sweats, and thoracic pain. Cough and dyspnea are severe. There is hemoptysis. The mucopurulent sputum may be of greater or lesser amount. Anemia and emaciation are frequently pronounced. On chest examination, there may be found areas of dullness with increased or diminished tactile fremitus due to consolidation or pleural thickening, bronchial or bronchovesicular breathing, or the breath sounds may be entirely absent, a few inconstant fine crepitations or many moist râles as well as an occasional pleuritic rub.

The course of the disease may be acute, but usually it is prolonged, with remissions and exacerbations, terminating in gradual deterioration or gradual recovery. Some of the intermediate types present the physical

signs of chronic bronchitis rather than of pulmonary tuberculosis. Others present the clinical picture of bronchial asthma. In a number of cases, occurring in different parts of the world, the course has been described as resembling pneumonia. Thus, rigors with high fever are mentioned in a few cases, and in several cases of acute onset the temperature fell by lysis after from eleven to fourteen days, convalescence following. Occasionally, sore throat and huskiness of voice appear as early symptoms. In one or two cases, inflamed tonsils are mentioned. Intense dyspnea is not infrequently noted. Balog and Grossi¹¹ ascribe the dyspnea and cyanosis in some cases to the accompanying myocarditis and decompensation of the right heart, which they attribute to the toxins of the monilia. These authors also mention pains in the lower limbs in cases of long duration.

The cough is paroxysmal, usually worse at night and in the morning. The sputum is sometimes scanty and difficult to raise, sometimes abundant. Except in the mild type of the disease, it is likely to be blood-streaked. It has been described as "like milk", later becoming curdly and pinkish, and again as grey, lumpy and gruel-like with a yeast-like taste. An odor is sometimes present in the breath, variously described as "like yeast" and "like beer fermentation". Castellani¹² remarks that the sputum may have an odor resembling that of commercial yeast. In examining sputum containing *Monilia metalondinensis*, Wheeler and Hoffstadt¹³ detected a yeast-like odor after a short period of incubation.

DIAGNOSIS

The diagnosis cannot be made at the bedside. It is based on (a) finding the fungus—yeast-like cells, more rarely mycelia—in the sputum, and (b) by culture. The species is determined by the specific fermentation of various sugars. The first essential is to obtain the sputum as fresh as possible after the patient has washed his mouth thoroughly with boiled or sterilized water. Castellani¹⁴ emphasizes the importance of having the patient gargle and rinse the mouth with sterile salt solution before being asked to cough or expectorate, because of the frequency with which the monilia fungi exist saprophytically in the mouth. He also stresses the necessity of immediate examination of the specimen in order to avoid air contamination.

Primarily, the diagnosis rests on the absence of tubercle bacilli and the presence of moniliae in the sputum, but cultural investigation and animal inoculation are also necessary. Castellani, Douglas and Thompson⁶ warn that a definite diagnosis of primary bronchomoniliasis should be made with great care and only when the bronchial expectoration, collected with every possible precaution, contains monilia in fair amount, tubercle bacilli being absent, and when the number of organisms decreases rapidly with the gradual improvement of the condition. Tuberculosis is excluded by the skin reaction, repeated absence of acid-fast bacilli in the sputum, and the biological tests. Syphilis and bronchial spirochetosis are excluded by serological tests and by examination for spirochetes. Other fungi are to be considered and looked for in cultures.

Animal inoculation, according to Castellani,¹⁴ provides the conclusive step. His criterion is that intrapulmonary injection into a rabbit must induce the characteristic numerous small white nodules, containing the fungus, in both lungs. It is not sufficient that an injection into the peritoneum or vein produce death in the animal with pneumonia and general septicemia, the strain present in the sputum must be shown to be capable of producing the characteristic lesions in the lungs. In the published cases of bronchopulmonary moniliasis this condition does not appear to have been fulfilled very generally. Some authors do not regard animal inoculation as essential to a final diagnosis.

Balog and Grossi⁸ reported testing eighteen patients who had pulmonary moniliasis, using scarification tests and intracutaneous and subcutaneous inoculations. Using as antigen an emulsion of the fungus killed by heat, they obtained only a general reaction which they interpreted as nonspecific. Thereafter, they employed emulsions made from living, untreated *Monilia pinoyi* Castellani which, they state, is strongly pneumotropic and does not harm the host when inoculated into the skin. With this living antigen intracutaneous inoculations were positive in all eighteen of the patients with pulmonary moniliasis and negative in all of the fifty-three controls consisting of normal healthy individuals or persons suffering from tuberculosis or other disease not due to monilia. The scarification tests were not successful, although intracutaneous tests made simultaneously in the same patients, were positive. In Steinfeld's¹⁰ study

of fifteen cases of bronchomycosis associated with certain types of bronchial asthma, intracutaneous reactions could not be interpreted

DIFFERENTIAL DIAGNOSIS

Differentiation from tuberculosis is as difficult as it is important. Mere absence of tubercle bacilli from the sputum is in itself not conclusive. The guinea pig inoculation test for tuberculosis must always be made. Roentgen examination is also important and should never be dispensed with, even though it serves only to rule out pulmonary carcinoma. It appears to be fairly characteristic of the roentgen picture in primary bronchopulmonary moniliasis that the apices remain clear, otherwise, the roentgenogram may correspond to that of tuberculosis in its various stages.

Frequently moniliae and tubercle bacilli are found together in the sputum. In that event, the monilia may be a saprophyte or there may be a true double infection. Balog and Grossi⁸ mention three cases in which they found that the symptoms clearly indicated the presence of the two diseases. They regarded the condition as a genuine moniliasis engrafted on a tuberculous base. Many writers on the subject look upon the fungus as a secondary invader when it is associated with the tubercle bacillus. A large number even assume that it may be disregarded from the therapeutic standpoint. That the fungus, appearing in abundance soon after infection, may antedate the tubercle bacillus in the sputum by months is not deemed significant of its priority as a causative agent. In general once the tu-

bercle bacillus has appeared, it is assumed that it represents the primary infection and bronchopulmonary moniliasis is assigned a secondary rôle.

The opinion, however, that the fungus infection is frequently the primary disease is not without supporters. Some feel that the ensuing pulmonary deterioration provides suitable soil for the subsequent lodgment of the tubercle bacilli. In support of this view Marett's observations are of interest. Ferguson¹⁷ cites Marett as saying that, in the Channel Islands, monilia infection of the lungs is as frequent as tuberculosis, and that most patients with tuberculosis have the double infection. Marett found "blastomycetes" alone in forty per cent of cases of suspected tuberculosis, "blastomycetes" and tubercle bacilli in forty per cent, and tubercle bacilli alone in twenty per cent. His experience led him to conclude that patients of the first class, if left untreated, soon pass into the second, a damaged lung being particularly susceptible to tuberculous infection, and that this second group has an outlook less hopeful than that of the third group who have only the pure tubercle bacillus infection. In order to avoid mixed infection in patients who have tuberculosis only, he urges their isolation from patients who have fungi as well as tubercle bacilli in the sputum. He finds that all cases of true double infection do best by treating the monilia infection first and then proceeding with the tubercle bacillus vaccine. In this, Balog and Grossi⁸ agree with him. Crank,¹⁸ who cites Marett's observations in connection with his own report of a case of bronchopulmonary moniliasis,

says "I think it probable that Colonel Marett has brought to light a truth unsuspected by his predecessors—that chronic blastomycetic bronchial catarrhs occur frequently and that they are the commonest precursors of tuberculosis in this country (England) "

The following is an illustrative case

M. B., aged 56, a merchant, first consulted the author in December, 1923, because of fever, cough, dyspnea, and pain in the chest

Past History Ten years before, he had had an attack of "pneumonia" and was confined to his bed for three months. Thereafter, he had had one or more attacks of "bronchitis" each winter. Tuberculosis was suspected each time, but in no instance were tubercle bacilli found in his sputum.

Present Illness The attack which began late in 1923 kept the patient in bed for a little more than one month. In addition to cough, dyspnea, and a pleuritic type of pain in the left chest, there was an irregular temperature ranging from 99° to 103°. The cough was paroxysmal and there was profuse expectoration of a yellowish mucoid material, occasionally blood-streaked. The respiration was rapid, varying from 30 to 40 per minute. The pulse rate ranged from 110 to 120. Examination of the chest revealed a leathery pleuritic friction sound over the entire left chest. Many moist râles were heard over both lungs, but were most numerous over the lower half of the left. Resonance was impaired, especially over both lower lobes, the impairment being somewhat more marked over the left. Several examinations of the sputum were made. All were negative for tubercle bacilli but *Monilia pulmonalis* was found each time, both on direct smear and in culture. An x-ray examination of the chest (see figure 1) showed extensive infiltration throughout both lungs, more marked on the left with both lower lobes especially involved. Iodide treatment was instituted and at the end of six weeks the patient was able to return to his business. He was, however, still short of breath on slight exertion and continued to have paroxysms of coughing.

Clinical Course He was not seen again for eighteen months. At that time he was having another attack of "bronchitis" similar in every respect to the one just described. The sputum was again negative for tubercle bacilli but *Monilia pulmonalis* was readily demonstrated as before. X-ray examination (see figure 2) now showed a diffuse infiltration of both lungs as before, but with considerably less involvement of the left lower lobe. The amount of lung involvement, on both examinations, was out of all proportion to the patient's symptoms and general appearance. The blood examination showed the following: Hemoglobin, 75 per cent, erythrocytes, 4,400,000, leucocytes, 8,150, polymorphonuclear neutrophils, 76 per cent, lymphocytes, 24 per cent.

Six months later, the patient had another attack which began in every respect like the many previous ones. There was the usual fever, pain in the chest, dyspnea, and cough with rather profuse expectoration. After a few days, areas of consolidation were found in the lower lobes of both lungs. Respiration became very labored and marked cyanosis appeared. The sputum contained considerable blood and was more tenacious than usual. Surprisingly enough, examination of the sputum showed many tubercle bacilli and many pneumococci. No moniliae were found in direct smear but they were grown in culture as before. The patient died at the end of two weeks, apparently from a bronchopneumonia. An autopsy was refused.

In such cases as this it is, of course, impossible to determine definitely which infection preceded. In this particular instance, however, it seems only reasonable to assume that there was a genuine primary moniliasis which provided suitable soil for the later invasion of the tubercle bacilli, the bronchopneumonia serving merely as a terminal event.

Balog and Grossi⁸ emphasize one important point of differentiation be-

tween primary pulmonary moniliasis and the secondary form accompanying tuberculosis. Cases of primary moniliasis of the lungs always show lesions of the base while lesions at the apex of the lungs, or extending to the apex, are identified as mixed forms of tuberculosis and moniliasis, the mycosis being regarded as a secondary infection. A second point of differentiation is that

in secondary moniliasis, the mucous membranes of the mouth, pharynx, and bronchi are usually invaded by the fungus. This is very rare in the primary type of lung infection.

In addition to a symbiotic action between monilia and the tubercle bacillus, other cases of mixed infection of the lungs have been reported. Secondary bronchomoniliasis is not infrequently met with in such cachectic

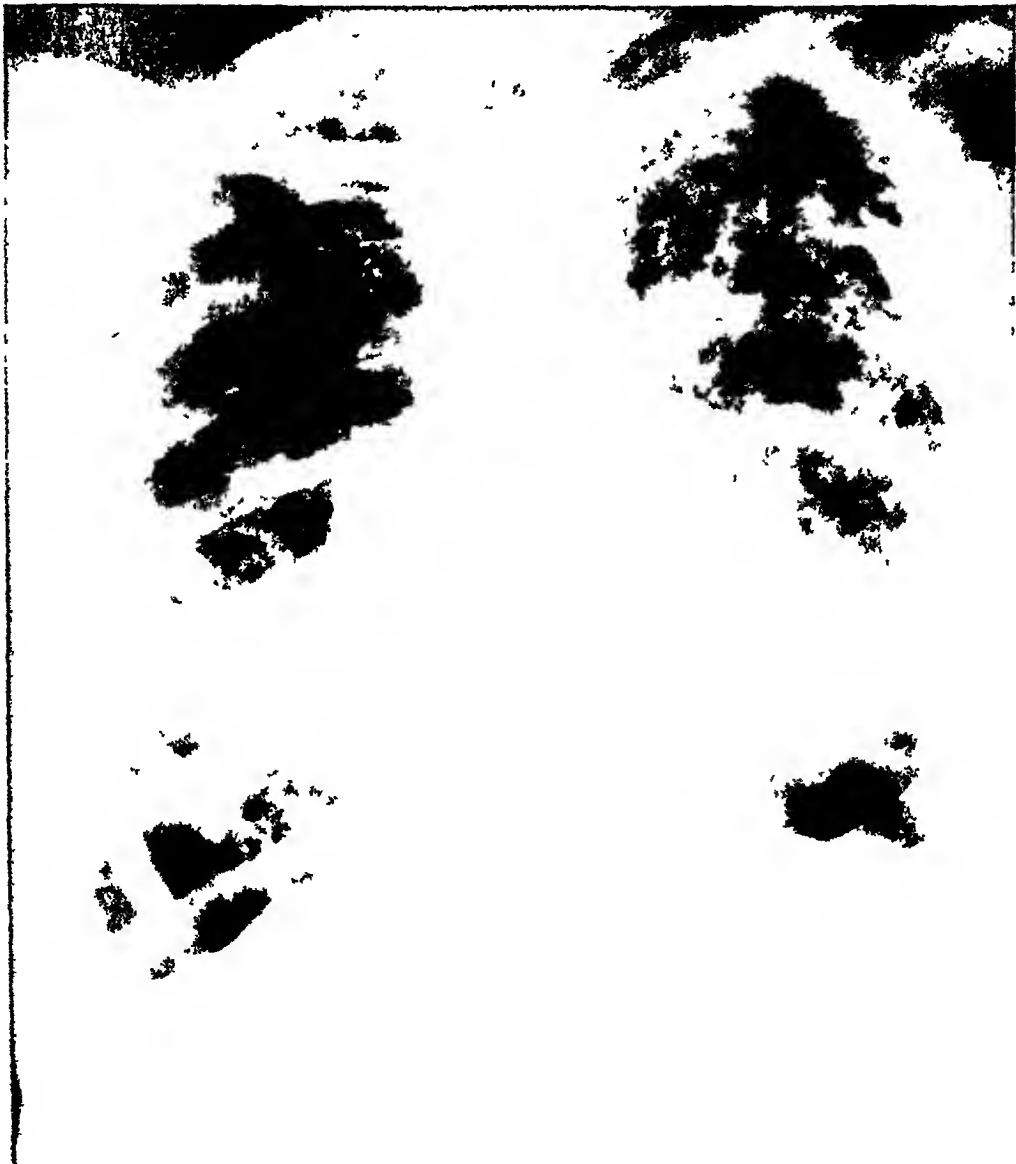


Fig. 1

FIG. 1. CASE 1, M. B. (Dec. 1923). Showing infiltration of both lungs, more extensive on the left and especially marked in the lower lobes.

diseases as cancer and diabetes. *Monilia* finds sugar-containing media particularly desirable soil.

The following case of pulmonary moniliasis occurred in a patient who also had syphilis. The relation between the monilia infection and the syphilis was always problematical.

W. W., male, aged 41, first came to the clinic in December, 1923, complaining of shortness of breath, cough and weakness.

Past History For fifteen years he had been troubled off and on with cough, much wheezing, and dyspnea on exertion. For three years these symptoms had been continuous. Occasionally he had had fever for several days at a time, and a few times the sputum had contained blood. Nevertheless, he had gained twenty-five pounds in weight. For several years he had been having hay fever with attacks of asthma, commencing in August and continuing until frost. Aside from his pulmonary symptoms his general health had been good. There was a fairly definite history of



FIG. 2. Case 1, M. B. (May, 1925). A diffuse infiltration of both lungs still present but a decided clearing of the left lower lobe.

syphilis, but he had considered himself cured

Present Illness At the time of consultation the patient related that the cough, wheezing and dyspnea, which had troubled him continuously for three years, were steadily growing worse and were accompanied by an increasing weakness. He had the appearance of a robust middle-aged man weighing about 200 pounds. His breathing was somewhat labored and examination of the chest revealed a moderate lagging of the left side with greatly impaired resonance over the left base. Many moist and wheezing râles were heard over the

lower half of both lungs, more on the left than the right. The heart sounds were obscured by the wheezing but were apparently normal. The blood pressure was 110/85, the pulse 86, and the respiration 24. The blood count was as follows: Hemoglobin, 90 per cent, leucocytes, 9,150, polymorphonuclear neutrophils, 68 per cent, lymphocytes, 32 per cent. The blood Wassermann was four plus positive. Urinalysis was essentially negative. Several sputum examinations were negative for tubercle bacilli. No cultures were made at this time.

Roentgenological examination of the chest (see figure 3) showed the left lung about



Fig. 3

FIG. 3. Case 2 W. W. (Dec. 1923). The left lung is about fifty per cent collapsed with multiple adhesions between visceral and parietal pleurae resulting in the formation of many pneumothorax pockets. Also an area of consolidation in the right lung shown.

fifty per cent collapsed with multiple adhesions between the visceral and parietal pleurae, resulting in the formation of many pneumothorax pockets. There was no free fluid, but there was an area of consolidation in the right cardiophrenic angle, with some mottling throughout the right upper and middle lobes giving the appearance of pulmonary tuberculosis. The heart and mediastinum were displaced to the left.

Clinical Course Because of the unusual lung findings, the negative sputum, and a strongly positive Wassermann, a tentative diagnosis of syphilis of the lungs was made and an intensive course of antisyphilitic treatment was commenced. Sulpharsphenamine, salicylate of mercury, and iodides were employed alternately. A month later the patient reported that he was much improved, was coughing less, and had less dyspnea. Three months after treatment had begun his general condition was greatly improved but there was no appreciable change in the pulmonary condition either on physical or x-ray examination. The sputum was again negative for tubercle bacilli and the blood Wassermann was still four plus positive.

After two months more of antileptic treatment he was coughing more and expectorating large amounts of yellowish purulent sputum, occasionally blood-streaked. He was having an irregular temperature, at times reaching 102°. He also complained of frequent attacks of a pleuritic type of pain in the right chest. The sputum was now cultured for the first time for possible fungi and *Monilia pulmonalis* was grown in large numbers. During the next twelve months, in addition to the routine antileptic treatment he was given iodides in large doses, both by mouth and intravenously. Under this treatment there was less cough and expectoration, less dyspnea, and a considerable gain in strength. The treatment was continued intermittently and about a year later the roentgenogram (see figure 4) showed that some re-expansion had occurred in the left lower lobe and in the base of the left upper with a diminution in the size of the pockets of pneumothorax. The left lung was still very poorly aerated, showing many areas of increased density, probably fibrosis. No change was apparent in the right

lung. Three months later, examination showed continued improvement but there was one large area of pneumothorax present in the left apex reaching down to the level of the second rib anteriorly. Still no change was seen in the right lung.

In the meantime, several sputum cultures had been made and the monilia was recovered each time. Finally, an autogenous monilia vaccine was given over a period of two months with no apparent benefit. The patient now passed into the hands of another physician who states that for the next three and one-half years the patient's condition was essentially unchanged and that, in spite of the cough and dyspnea, he was able to carry on his work as a traveling salesman. Several sputum examinations were made for tubercle bacilli, all of which were negative. In December, 1929, he developed influenza to which he succumbed in three days.

Mixed infections with two different fungi are occasionally met with. Cases of mixed monilia and anaeromyces infection have been described by Castellani, Douglas and Thompson,⁶ and of monilia and spirochetes by Castellani.¹⁴ They base their belief that each was playing an etiologic rôle on the cure obtained by combining the treatments for the two conditions after treatment for each separately had failed. They suggest that when a mild or moderately severe case of bronchomoniliasis fails to respond to potassium iodide and creosote, mixed infection should be considered and a second organism looked for.

Cases of bronchitis and bronchial asthma, pneumonia, pseudodiphtheria, cancer of the lung, phthisis tuberculosis of the axillary lymph glands, glycosuria, diabetes bronchospirochetosis, anaeromycosis, thrush and dermatitis have all been mentioned in which a more or less important rôle is ascribed to monilia. In its primary

form bronchopulmonary moniliasis should be promptly differentiated, especially from tuberculosis. Even when secondary, it should not be neglected, for it only prolongs the course of the original process and causes further damage.

CLINICAL PATHOLOGY

The moniliae belong to the family of hyphomycetes. There are many varieties. Castellani¹ alone has isolated more than forty species and

others have added to this number. The Genus *Monilia* is characterized by sporophores which are simple or sub-simple and proceed by constriction at their extremities, and by a chain of large lemon-shaped conidia often provided with a disjunctive apparatus. The tendency has been, however, according to Castellani, Douglas and Thompson,⁶ to include under the term "monilia" all the organisms of the family Oosporaceae Saccardo, 1886. The lack of definitely fixed biological re-

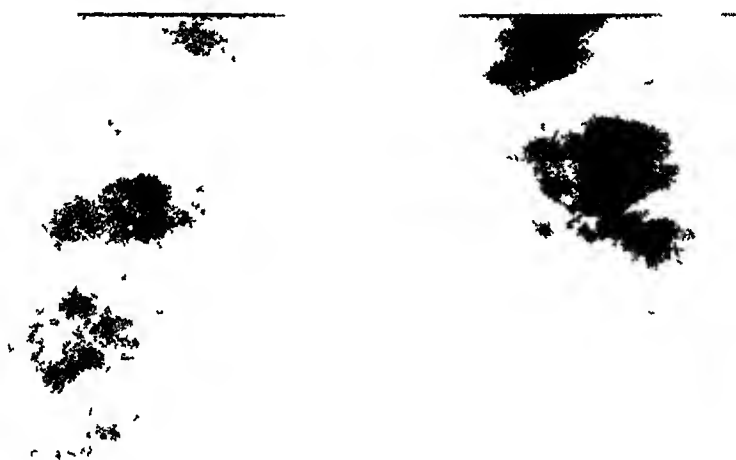


Fig. 4

Fig. 4. Case 2. W. W. (Mar. 1925). Some re-expansion had occurred in the left lower lobe, with a decrease in size of the pneumothorax pockets except the one at the apex. No change was apparent on the right.

relationships in the field of the yeast fungi has been mentioned in a foregoing paragraph. When isolated from lesions monilia presents microscopically a vegetable body composed of mycelial filaments of somewhat large size, frequently having arthrospores and numerous free oval or somewhat round "buttons." When grown in cultures, especially on solid media, the organism consists exclusively of oval or somewhat round "buttons." It grows well on solid or liquid media containing glucose or maltose.

In making cultures the greatest care must be exercised to exclude the ordinary saprophytic mouth fungi. Castellani's¹⁴ method is to cleanse the mouth with a wash of a 1:5000 solution of potassium permanganate. The patient then expectorates into a sterile Petri dish. The sputum is inoculated on plain broth, agar and glucose broth. These are incubated at room and incubator temperatures. At the same time, the sputum is examined for protozoa and tubercle bacilli. After forty-eight hours, white colonies, milky in appearance with "cupola" tops, are selected and examined microscopically. The presence of conoid forms about the size of a red blood corpuscle confirms the presence of some species of monilia. Passing the culture through a series of sugars completes the classification of the parasite.

Identification of monilia in direct smears of sputum is by no means easy unless the fungi are present in very large numbers. Piper¹⁰ finds the resemblance of the oval spores to the nuclei of body cells or even chromocytes very misleading. He mentions a differential stain which he has found

highly satisfactory. In examining the fresh sputum, spirochetes are ruled out by means of dark ground illumination, lung parasites, such as *Paragonimus ingeri* (Cobbold, 1880), by simple microscopical examination, and tubercle bacilli and the acid-fast species of *Nocardia* are distinguished by one of the usual methods of demonstrating acid-fast bacilli. The presence of non-acid-fast species of *Nocardia* and of yeast-like fungi is revealed by coloring films of the fresh sputum by Leishman's and Cram's methods.

The blood findings vary considerably, many investigators finding no important changes in the blood picture while others report marked variations. Some degree of anemia appears to be the rule. A slight leukocytosis has been mentioned a few times, and eosinophilia is frequent.

Complement fixation reactions with the sera of patients have been obtained in some instances, notably in the cases reported by Farah,¹⁰ Kurotchkin and Chu,²⁰ and Hoffstadt and Lingenfelte.²¹ Steinfield¹⁶ found the complement fixation reaction of equivocal value, and concluded that the agglutination reaction gave no new information. Peruchena's²² agglutination experiments with normal and immune sera were negative. In Parise's²³ case the organism was not agglutinated by the patient's serum. Farah,¹⁰ however, found that the fungus gave a positive agglutination reaction with the patient's serum and Hoffstadt and Lingenfelte²¹ noted that this organism showed spontaneous agglutination. A positive precipitin reaction was obtained by Kurotchkin and Chu²⁰ when the patient's serum

was added to various extracts of monilia cells, and control sera were negative. Peruchena's²² attempts to produce hemolysis with cultures failed.

Roentgen examination is of value in all cases. It shows definitely the location of the infection and its progress. A general characteristic of genuine primary bronchopulmonary moniliasis is that the apices remain clear, even in advanced cases. The x-ray also serves to rule out pulmonary carcinoma, and when used in conjunction with lipiodol injections, to exclude bronchiectasis.

Very few postmortem examinations have been reported. A review of the literature on bronchomoniliasis reveals only five authors²⁴ who mention autopsies. The only report of a postmortem examination made in the United States appeared from Baltimore in 1916 when Boggs and Pincoffs³ described the first case of pulmonary moniliasis published in medical literature in this country. The case report appearing at the conclusion of this paper contains a detailed account of the postmortem findings in the author's case of primary bronchopulmonary moniliasis in which *Monilia pulmonalis* was demonstrated repeatedly in the sputum, both on direct smear and on culture. Repeated examinations for tubercle bacilli were always negative.

PATHOLOGY IN EXPERIMENTAL ANIMALS

Castellani¹⁴ found that the virulence of different moniliae varies, i.e., (a) a few strains are non-virulent to laboratory animals, (b) certain ones are virulent and will kill a rabbit or a guinea pig following intravenous or in-

trapulmonary inoculation, but without the evident pseudotubercular nodular condition of the lung; (c) others produce a peculiar nodular condition both in the inoculated and in the non-inoculated lung, when injected intrapulmonarily and at times intravenously.

If the monilia isolated from the sputum is nonpathogenic, intrapulmonary inoculation in rabbits produces neither lung lesions nor general infection. When the fungus is virulent but only a secondary invader, intravenous injection will kill the rabbit and intrapulmonary injection will induce a fatal septicemia, but without a localized nodular affection of the lungs. When the monilia is the real cause of a broncho-alveolar condition, intrapulmonary injection will produce in the rabbit a very characteristic nodular condition of the lungs, both lungs becoming studded after two or three weeks with a large number of white nodules which contain the fungus. Some of these nodules may coalesce, forming a staphyloid mass. The smaller nodules are about one-eighth of an inch in diameter and microscopically, contain in their centers masses of small white cells and polymorphonuclear leukocytes which decrease in number peripherally. They are in turn surrounded by a ring of epithelial cells, many containing phagocytized smaller white cells, together with a few large multinucleated giant cells. At times the cells in the center of the nodules are markedly degenerated, the nodules there showing gross caseation. In most instances there is some congestion but no pneumonia between the nodules. Thickening of the intima is present in the small arteries

Castellani¹⁴ maintains that the demonstration of the characteristic nodular condition in the lungs is essential for the establishment of the diagnosis of primary bronchopulmonary moniliasis, while other writers contend that animal inoculation is not even necessary when the sputum is repeatedly positive for monilia.

In their animal experiments, Balog and Gross¹⁸ used an emulsion of living mycetes. Intrapulmonary inoculation, as first done by Castellani, they found to be the most efficacious method of injection. They give an excellent description of the lung changes following intrapulmonary inoculation in rats of a strain capable of producing pulmonary disease, and note the remarkable likeness to tuberculosis. Intracardiac inoculation into guinea pigs resulted in death from acute septicemia. Kurotchkin and Chu²⁰ found that intrapulmonary inoculation of *Monilia tropicalis* did not kill the rabbit in from three to five weeks, but invariably produced extensive necrosis in the lung with obliteration of the pleural cavity and formation of a few nodules. Intravenous and intraperitoneal inoculation killed with mycotic septicemia, small disseminated whitish nodules containing the monilia appearing in the lungs and other organs. In general, intravenous inoculation with a virulent strain produces general septicemia, nodules may appear in various organs, with or without simultaneous lung involvement. Intraperitoneal inoculation may or may not succeed.

PROGNOSIS

The mild type of bronchomoniliasis may result in spontaneous cure

and is always readily amenable to specific treatment. Usually the intermediate type also yields to treatment, but the response is slow. A prolonged course of treatment is often necessary. Sometimes this type apparently remains stationary, but, if neglected, it not infrequently passes into the severe form. Except perhaps in its early stages, the severe type is usually incurable, although death may not take place for many months.

Chyruha²⁵ presents from Venice a good example of the chronic intermediate type of the disease. A more severe form which, nevertheless, seems to have changed little over a period of ten years is described in detail by Galbreath and Weiss² from Porto Rico. Colard and Jauman²⁶ of Belgium describe a case which presents the progressive type. In one of five cases, reported by Stovall and Greeley²⁷ from Wisconsin, the course was rapid, death ensuing in four weeks. This case appears to have been of the severe type from the beginning. The case report which appears at the conclusion of this article illustrates the severe type of the disease.

TREATMENT

The treatment of bronchomoniliasis is based upon the specific germicidal effect of potassium iodide on monilia. This drug has had such beneficial effect particularly in the mild and intermediate cases that it has come to be regarded as the specific. In severe cases however it appears to be of little, if any value. In such cases lipiodol by intratracheal injection deserves extended trial. This may be combined with intramuscular injection

tions Castellani^{6,14} advises that potassium iodide be given in fifteen grain doses in milk or water three times a day, this treatment requiring three or four weeks to effect a cure in mild cases. In addition, he advises creosote, glycerophosphates and balsamics, and tonics to combat the loss of appetite and the anemia. He has found that cases of mixed infection, as for example moniliasis and anaeromycosis, are frequently cured by combining the treatments for the two infections. When possible, the patient who lives in a hot moist part of the world should be removed to a more suitable climate.

Stovall and Greeley²⁷ treated one case with intravenous injections of gentian violet, and saw much improvement. Balog and Grossi⁸ believe that insulin is of value, even in cases without glycosuria. Farah¹⁰ states that pneumosan injections may prove useful. He recommends lipiodol—forty per cent iodine in poppy oil—(2 cc) injected intramuscularly in the gluteal region on alternate days, as this treatment appears to be useful in early stages before there is serious damage to the lungs. Energetic treatment, using "iodides, autovaccine (Stemfeld's method), alkalines by mouth, ultraviolet rays, etc.", produced good results in the chronic case Chyurha⁵ reported from Venice. In Nasso's²⁸ case of a child who had previously had malaria, despite a negative search for plasmodia, the patient improved under intensive quinine treatment. Craik¹² treated his patient successfully with alkaline potassium iodide and adrenal-
in.

In their case from the Belgian Congo, which had progressed rapidly,

and was in an advanced stage when the patient came under their observation, Colard and Jaumain²⁶ used injections of oil containing iodoform, eucalyptus, and creosote, and intravenous injections of sodium cacodylate and potassium iodide by mouth, all without result. Because of respiratory difficulties artificial pneumothorax had to be discontinued, and because of the venous sclerosis induced, intramuscular injections of Lugol's solution, 6 cc per day, had to be substituted for the intravenous injections. Local applications to the buccopharyngeal lesions were powerless to check their advance. All treatment was unavailing.

Satisfactory results from small doses of roentgen rays in ten cases of bronchomycosis have been reported by Howe and Schmidt,²⁹ but they do not state the kind of fungus involved. Among their patients were two bakers, each having considerable yeast in the sputum. Both were helped by x-ray treatments.

Vaccine treatment has had varying success. Of the forty-three cases Pijper¹⁹ mentions, sixteen were treated with autogenous vaccines only, the doses ranging from fifty million cells to two thousand million cells. Very good results were obtained in three cases and there was distinct improvement in three others, but in the remaining ten cases there was no improvement. This author believes that iodine should be given in addition to the vaccine. Kotks, Wachowiak and Fleischer¹ saw complete disappearance of symptoms following the use of autogenous vaccine in one case, and great improvement in another before it passed out of control. In Stemfeld's¹⁶

fifteen cases, iodides were efficacious and vaccines, prepared from organisms killed by heat, dose 0.1 cc increasing to 1.0 cc, seemed to help. For therapeutic purposes Balog and Grossi¹¹ used the same emulsion of living, untreated *Mompha pinoi* Castellani as for diagnostic skin tests. By repeated injections with progressively increasing doses, they were able to effect healing in a short time in most cases and to produce great improvement in the remainder. They note that monilia vaccine therapy always acts gently and that desensitization takes place during the treatment. They have found vaccine treatment the only therapy which restores the myocardium after injury by the monilia toxins.

CASE REPORT WITH POSTMORTEM FINDINGS

Mrs. J. H. T., aged 38, the mother of four healthy children, the youngest five years of age, first consulted us in October, 1923, because of fever, cough, and occasional hoarseness.

Family History. The family history was negative.

Past History. The patient had lived in Memphis for the preceding eleven years, prior to that she had lived in Virginia and in Washington, D. C. She had influenza during the epidemic of 1918 and typhoid fever in 1919. In 1920 she had an attack of pleurisy with effusion, apparently with complete recovery. The chest was aspirated at that time but no bacteriological examination of the fluid was made. The following spring (1921) she had a second attack of pleurisy for which she consulted a well known internist in the East who diagnosed pulmonary tuberculosis although sputum examination was negative for tubercle bacilli. Within a few weeks she was free from fever and for the next eighteen months considered herself well.

Present Illness. During the early spring of 1923 she began to complain of cough and hoarseness, and a few times expectorated blood-streaked sputum, but she did not consult a physician. Her weight had remained practically stationary since the attack of typhoid fever four years before, but there had been a noticeable lack of endurance and some shortness of breath on exertion. It was of these symptoms as well as of cough, hemoptysis, hoarseness, and slight fever that she complained when she first consulted us. There were no digestive or urinary symptoms. Her menstruation was normal and regular.

Physical Examination. The patient was a well developed and well nourished middle-aged woman weighing 160 pounds. Her color was normal and she did not look ill. The tonsils were somewhat enlarged and showed evidence of chronic infection. The general physical examination was otherwise essentially negative except for the chest findings.

Chest. Expansion of the left side was diminished. Over the lower part of the left upper lobe and over all of the left lower lobe there was marked dullness and decreased tactile fremitus. Over this area there were moist râles and diminished breath sounds. Both apices were apparently clear but there was an area of dullness without râles in the right axilla. There were no areas of tenderness to pressure.

Heart. The apex beat was neither visible nor palpable. The area of cardiac dullness blended with that of the lung dullness. The heart sounds and rhythm were normal. The blood pressure was 120/80, and the pulse 82.

Clinical Course. In spite of a negative sputum examination we concurred in the previous diagnosis of pulmonary tuberculosis and considered it of the fibroid type. A few weeks later the patient entered a well known tuberculosis sanatorium in North Carolina where she remained for eight months. While there her temperature remained normal except for an occasional slight rise following an injection of tuberculin. Her cough and hoarseness practically disappeared and she gained several pounds in weight. During her stay in the sanatorium repeated sputum examinations were

made for tubercle bacilli all of which were negative. No other bacteriological studies were made. In spite of this clinical improvement x-ray examination showed a definite increase in the area of infiltration in the lungs.

The patient returned to Memphis on July 4, 1924. She looked and felt well. The next day she had a rigor followed by temperature of 103°. In a few hours there developed a pain of pleuritic type in the left

chest posteriorly. The following day she was coughing considerably and the sputum was streaked with bright blood. Examination of her chest showed marked dullness throughout the left lung from the level of the third rib to the base, with diminished breath sounds and tactile fremitus. Moist râles were heard over both lungs but there were more over the left than the right and more over the lower than the upper lobes. Respiration was 36 and the pulse



Fig. 5

Fig. 5. Case 3 Mrs. J. H. L. (Oct., 1923). Showing a marked homogeneous density involving the lower half of the left lung, with the mediastinum displaced to the left. In the upper portion of the right lung are two areas of similar density, roughly triangular in shape, which seem to be peripheral and apex toward the center of the lung. Both apices

was 120. For the next ten days she was critically ill, her temperature ranged from 100° to 103°. At the end of two weeks the temperature was normal in the mornings but continued to rise in the afternoons to 101°. The dulness over the left base increased and a possible pleural effusion was suspected. The chest was aspirated but nothing was obtained. The sputum was persistently negative for tubercle bacilli. The total and differential blood count remained normal.

Two months later the general condition of the patient showed very little change. She was still having an afternoon temperature, and the cough and the quantity of expectoration had increased. She had apparently gained in weight but was becoming more dyspneic and had to sleep most of the time on three pillows. She was most comfortable when lying on the left side. Chest examination now showed considerable dulness and more moist râles over the right lower and middle lobes. The right upper lobe and the upper half of the left upper lobe remained apparently clear.

In the meantime, repeated cultural studies of the sputum for fungi had been made and each time there was obtained a pure growth of *Monilia pulmonalis* Castellani. Convinced that we were not dealing with tuberculosis, we commenced the administration of iodides in large doses, at first by mouth and later intravenously. The only noticeable effect of this treatment was a marked increase in the quantity of sputum, in which an occasional streak of blood continued to appear. Sodium cacodylate was then tried, both intramuscularly and intravenously, but to no avail.

Finally, with both lungs apparently solidified except the right upper lobe and the apex of the left upper, the dyspnea was so great that the patient was compelled to sit upright to breathe. There was considerable cyanosis and a moderate amount of subcutaneous edema. The temperature continued to range from 99° to 101°, the pulse and respiration gradually increasing. But, withal, there was no apparent loss of weight and but little anemia. Death occurred on December 24, 1924.

Röntgenological Findings The first x-ray examination, made October 2, 1923 (see figure 5), showed a marked and fairly homogeneous density throughout the left lower lobe which blended with the heart shadow. The mediastinum and the heart were displaced to the left. The upper margins of the density were fringed and invasive in appearance. In the periphery of the right lung there were noted two areas of similar density, both roughly triangular in shape with bases at the periphery and apices toward the center of the lung field, the upper and smaller area seemed to be situated in the lower part of the upper lobe, while the larger area seemed to be in the adjacent part of the lower lobe. The apices of both lungs were strikingly clear.

Five weeks later (see figure 6), the areas in the right lung had increased in size and were becoming more confluent. The density in the left lung had extended upward, especially at the periphery. No new areas were noted. Seven months later (see figure 7), the heart and mediastinum were displaced further to the left, and the upper lobe was so encroached upon, both from the mediastinum and from the invasion below, that only a small portion appeared to be air-bearing. The two coalescing areas in the right side now extended from the periphery to the mediastinum and seemed to involve all of the middle lobe as well as the lower part of the upper lobe. That part of the shadow corresponding to the lower part of the upper lobe showed a lighter central area suggesting cavitation. Several new small areas of density now appeared in the right lower lobe.

The last x-ray examination was made October 2, 1924 (see figure 8), exactly one year from the date of the first observation. The only important changes were found in the right lower lobe, where the areas of density had enlarged and coalesced until the peripheral half of the lobe seemed to be consolidated. Only about one-third of the lungs remained ventilated.

Laboratory Findings When first examined (October, 1923) Blood Hemoglobin, 90 per cent, leucocytes, 7,150, polymorphonuclear neutrophils, 66 per cent,

lymphocytes, 33 per cent, eosinophils, 1 per cent The blood Wassermann was negative Urinalysis was negative Two sputum examinations were negative for tubercle bacilli, no cultures were made

After return from sanatorium (July, 1924) Blood Hemoglobin, 90 per cent, erythrocytes, 4,670,000, leucocytes, 10,200, polymorphonuclear neutrophils, 70 per cent, lymphocytes, 27 per cent, eosinophils 3 per cent Urinalysis was negative The sputum was repeatedly cultured at this time for fungi and always *Monilia pulmonalis*

Castellani was obtained in practically pure growth Oval yeast-like cells with a few club-shaped segments were found every time in direct smears These were Gram positive An abundant smooth white growth developed on all the usual media The same kind of oval cells were found in smears, and as the growth aged and assumed a "fluffy" appearance, bits of mycelium were found Both continued to be Gram positive Broth remained clear at first and then a thin pellicle formed Acid and gas were negative on inulin, dulcrite,



FIG 4

FIG 4. Case 3 Mrs J. H. F. (Nov. 1923) The areas of density in the right lung had increased in size and were becoming confluent The density of the left lung had decreased and the area of density was smaller than before

and lactose, but at first they were positive on maltose, glucose, and saccharose. There was no gas and very little acid on mannite. As subculturing was continued acid and gas were not produced in any of the sugars. Simultaneous examinations for tubercle bacilli were negative.

An autopsy was performed and cultures were made from the lungs about four hours after the body had been embalmed, but no growth was obtained.

Autopsy Findings Examination was limited to the thorax and abdomen.

Lungs The left lung was reduced to one-third normal size, and adhered closely to the chest wall, held by dense fibrous adhesions of firm consistency and difficult to tear. The visceral pleura in several places was more than 3 cm in thickness and of the consistency of tough connective tissue. The delivered lung presented a ragged appearance, produced by tags of fibrous adhesions.



FIG 7, Case 3, Mrs J H T (June, 1924) The mediastinum is displaced further to the left and only a small portion of the left upper lobe remains clear. The density in the right lung now extended from the periphery to the mediastinum, and some smaller areas had appeared at the right base. Both apices still clear. (For this roentgenogram we are indebted to Dr C P Ambler, Asheville, N C.)

The substance was quite resistant to cutting and its surface presented numerous small cavities rather uniformly distributed. The largest was about 4 cm in diameter, and each connected with a bronchus. These gave the lung a cheese-like appearance. Most of these cavities were smoothly lined and many were filled with a clear jelly-like material. There was but little air-bearing tissue in either lobe. The large blood vessels were moderately thickened. The

lymph-nodes were small, pigmented black, and only one contained lime salts.

The right lung was increased in size, was less firmly adherent to the chest wall than the left, and presented a pale mottled appearance. The visceral pleura was slightly thickened. Only parts of the upper and middle lobes were crepitant. On the cut surface a few cavities were found. These resembled closely those found in the left lung as to size, lining and contents, while



Fig. 8

Fig. 8. Case of Virus J. H. I. (Oct. 1924). The areas of density in the right lower peripheral half of the lobe. Not much change

the remainder of the lung substance was consolidated as in pneumonia but differed in gross appearance. The consolidated portion was easily torn. The torn margins resembled frogs' eggs in shape and consistency. The entire cut surface presented a glistening, shiny, grayish, translucent appearance not unlike that of a colloid carcinoma. The entire right lung, except a portion of the middle lobe and the apex of the upper lobe, was consolidated. It was estimated that less than fifteen per cent of the lung was air-bearing.

Heart The pericardial sac was drawn to the left by neighboring adhesions. The heart and vessels were otherwise normal in every respect. The aorta presented a few linear patchy areas of intimal thickening.

Liver The liver was slightly enlarged and the cut surface had the appearance of passive congestion.

Spleen The spleen was about normal in size and consistency. The cut surface presented several small firm tubercle-like bodies.

Other Organs The other abdominal and pelvic organs were essentially normal.

Microscopical Findings were as follows.

Lungs The bronchial epithelium was usually denuded—that which remained showed metaplasia. The bronchial walls were necrotic and infiltrated with mononuclear wandering cells and lymphocytes with an occasional red cell and polymorphonuclear leucocyte. This infiltration extended from the bronchial walls to the immediately surrounding alveoli. The remaining alveoli were characterized by the following changes:

(1) The filling and dilatation of the entire alveolus with serum albumin. (2) The presence of a fibrin-like material occupying the alveolus with the exception of an area subjacent to the alveolar epithelium. Embedded in this fibrin-like material were peculiar large pale cells of different sizes and shapes, with unusually well defined cell membranes. There were definite connections between the fibrin-like material and the cell membranes. These cells were usually round, at times oval, but in the very large empty forms, pseudopodia-like structures occurred. The cytoplasm stained very

pale, was reticular, granular or stippled, but occasionally crescentic-shaped forms occurred, formed by large clear empty spaces which crowded the nucleus and the cytoplasm to one end of the cell. The nuclei were leptochromatic but large and occupied about one-half of the cell space. Some cells contained two small nuclei. An occasional cell was found with pyknotic nucleus but without cytoplasm. (3) The occurrence of syncytial masses in the same alveolus with the fibrin-like material described above, but distinct and separate therefrom, usually lying at one end of the alveolus and but rarely in its center. They stained dark red and were large, round, kidney shaped or crescentic. In the smaller masses the nuclear structure was distinct and well defined while in the larger ones the nuclei were less well preserved and very poor in chromatin. The nuclei occurred in the center or the periphery of a mass.

The alveolar walls, especially about the larger bronchial vessels, were infiltrated with the same types of cells. Their vessels were engorged with red blood cells, but necrosis and rupture of their walls were also present. In some areas, compression atelectasis was prominent. The large pale cells previously described were to be found lining some of the alveoli, at times in aggregate nuclear masses. The lung tissue, subjacent to the pleura, was characterized by fibrosis, with an occasional small area of necrosis or infiltration with mononuclear wandering cells.

Lymph Glands The lymph glands showed diminution in size of the cortical germinal centers and widening of the pulp medullary spaces with increase of the latter's contents.

We are indebted to Miss Florence M. Frost, formerly Director of Laboratories of the Polyclinic, for the careful cultural studies and for their description in this case. For performing the autopsy and for the description of the findings we are indebted to Dr. J. A. McIntosh, who was at the time Associate Professor of Pathology in the College of Medicine of the University of Tennessee. We desire also to express our appreciation to Dr. I. D. Michelson, emi-

nent mycologist and Professor of Bacteriology in the College of Medicine of the University of Tennessee, for the description of the microscopical findings, and for his invaluable assistance and helpful criticism in the preparation of this paper

DISCUSSION

In Case 1 the monilia infection apparently antedated the invasion of the tubercle bacilli. In Case 2 it is doubtful whether any direct relation existed between the moniliasis and the syphilis. Case 3 was apparently complicated by no concomitant factor, even though treated for many months as tuberculosis and preceded by influenza and pleurisy. It illustrates many of the salient features to be considered in dealing with fungus infection, emphasizing the importance of early recognition, of prompt differentiation, particularly from tuberculosis, and of repeated bacteriological and roentgen examinations. A unique feature in this case was the very sudden onset of the acute stage which continued unabated to a fatal termination in a relatively short time. In two cases of rather advanced tuberculosis, not mentioned in this series we were able to demonstrate *Monilia pulmonalis* in the sputum and in these cases we believe the yeast-like organisms were essentially secondary invaders.

It seems reasonable to assume that the monilia is a secondary invader although it may be the chief factor in maintaining the chronicity of symptoms in some types of pulmonary disease. As Procházka, Kotkis, Wachowicz and Forsher¹ and other writers have suggested it is quite possible that

some irritant agent, bacterial, toxic or mechanical, may initiate in the mucosa of the bronchus certain changes which make it possible for the monilia not only to maintain its existence but to grow. If these assumptions are correct, we may have to interpret bronchomoniliasis and probably many other types of bronchomycosis as conditions in which a primary factor, either still active or no longer acting, has initiated certain changes which have permitted the fungi to gain foothold and to find more or less permanent lodgment in the bronchi. The numerous cases, such as Case 3, in which a preceding bronchitis, influenza, pleurisy or pneumonia is mentioned, suggest a lowered resistance of the host, thus providing a suitable soil for the development of these fungi. We must concede that, once established, they are capable of becoming and not infrequently do become the essential and important element in maintaining the irritation in the lesions which they invade. In studying such cases we should as a rule look beyond the relatively avirulent moniliae, without in any way ignoring the rôle of these fungi for some other possible factor in the causation of the chronic inflammation. Also, we should certainly study very carefully all cases of chronic bronchitis, tuberculosis of the lungs and other pulmonary diseases of long duration especially those which in any way run a peculiar clinical course, and in such cases should insist upon repeated bacteriological examinations for fungi.

REFERENCES

- ¹IACONO, I La moniliasi bronchiale del Castellani, *Riforma med*, 1922, xxxviii, 303
- ²GALBREATH, W R, and WEISS, CHARLES Bronchomoniliasis, *Arch Int Med*, 1928, xlii, 500
- ³BOGGS, THOMAS R and PINCOFFS, M C A case of pulmonary moniliasis in the United States, *Johns Hopkins Hosp Bull*, 1915, xxvi, 407, also *Johns Hopkins Hosp Rep*, 1916, xvii, 63
- ⁴SIMON, STEINFELD, JOHNS, KOTKIS, WACHOWIAK and FLEISHER, WALLACE and TANNER, SHAW, STOVALL and GREELEY, HOFFSTADT and LINGENFELTER, WHEELER and HOFFSTADT, GILBERT and GROESBECK, STOKES, KISER and SMITH
- ⁵CASTELLANI, ALDO, and CHALMERS, ALBERT, J *Manual of Trop Med*, ed 2, 1913, 822
- ⁶CASTELLANI, ALDO, DOUGLAS, MACKENZIE, and THOMPSON, E T Notes on mixed mycotic infections, *Jr Trop Med and Hyg*, 1925, xxviii, 257
- ⁷PROCHAZKA, KARL Die Pathogenese der Blastomykosen, *Arch f Dermat u Syph*, 1925, cxlix, 511
- ⁸GROSSI, GINO, and BALOG, PAUL Clinical and experimental studies in Castellani's pulmonary moniliasis, *Jr Trop Med and Hyg*, 1929, xxxii, 253
- ⁹KOTKIS, A J, WACHOWIAK, M, and FLEISHER, MOYER S The relation of monilia to infections of the upper air passages, *Arch Int Med*, 1926, xxxviii, 217
- ¹⁰FARAH, NAJIB Observations on Castellani's bronchomoniliasis, with report of a case with pneumonic onset and a peculiar clinical course, *Jr Trop Med and Hyg*, 1923, xxvi, 1
- ¹¹BALOG, PAUL, and GROSSI, GINO Allergie der Haut bei Lungenmoniliasis, *Arch f Dermat u Syph*, 1929, clvii, 549
- ¹²MAUTNER, H Eine bisher nicht beobachtete Moniliaart bei chronischer Bronchitis, *Wien med Wchnschr*, 1914, lvi, 1065
- ¹³DR ALMIDA, FLORIANO PAULO, and DOS SANTOS, LOURIVAL F Sobre um caso de "Blastomycose" pulmonar, *Annaes da Faculdade de São Paulo*, 1927, ii, 221
- ¹⁴CASTELLANI, ALDO Hemorrhagic bronchitis of non-tubercular origin, *Proc Internat Conference on Health Problems in Trop Am*, United Fruit Co, Boston, 1924, p 847 Id *Bronchomycoses*, *Jr State Med*, 1926, xxxiv, 202 Id *Fungi and Fungus Diseases* (Adolph Gehrmann Lectures), *Am Med Assoc*, 1927-28, also *Arch Dermat and Syph*, Oct, 1927 to Mar, 1928 Id *Internal Mycoses*, *Med Clin N Am*, 1928, vi, 1123
- ¹⁵WHEELER, HOMER, and HOFFSTADT, RACHEL E Bronchomoniliasis caused by *Monilia metaloudensis*, *Jr Lab and Clin Med*, 1929, xv, 122
- ¹⁶STEINFELD, EDWARD Bronchomycosis associated with certain types of bronchial asthma, *Jr Am Med Assoc*, 1924, lxxxii, 83
- ¹⁷FERGUSON, ARNOLD S Blastomycosis of eye and face secondary to lung infection, *Brit Med Jr*, 1928, i, 442
- ¹⁸CRAIK, ROBERT Moniliasis and tuberculosis, *Brit Med Jr*, 1929, i, 682
- ¹⁹PIJPER, A Moniliasis, *Med Jr S Africa*, 1917, xii, 129 Id *Bronchomoniliasis and monilia fungus in the sputum*, *Med Jr S Africa*, 1923, xiv, 101
- ²⁰KUROTCHIK, T J, and CHU, C K Bronchomoniliasis Serological studies on a case, *Nat Med Jr, China*, 1929, xv, 403
- ²¹HOFFSTADT, RACHEL E and LINGENFELTER, JOHN S A pulmonary infection caused by *Monilia balcanica* (Castellani), *Am Jr Trop Med*, 1929, vi, 461
- ²²PERCINIA, JOSÉ G Sobre um caso de moniliasis pulmonar, *Semana med* 1929, xxxvi 527
- ²³PARISE, NICOLA Contributo sulla moniliasis simulatrice di tubercolosi pulmonare *Riforma med*, 1923, xxxix 241
- ²⁴JOFFES and SIMPSON REDFERN MACLEOD and ICKHAM MENDISON BOGGS and PINCOFFS

- ²⁵CHAUURLIA, N Notes on a case of bronchomycosis, Jr Trop Med and Hyg, 1926, xxix, 145
- ²⁶COLARD, A, and JAUMAIN, D Sur un cas de moniliasse pulmonaire, Bruxelles-Méd, 1925, v, 1503
- ²⁷STOVALL, W D, and GRELLEY, HUGH P Bronchomycosis, Jr Am Med Assoc, 1928, xci, 1346
- ²⁸NASSO, Ivo Un caso di bronchomoniliasi, Pediatria, 1926, xxxiv, 37
- ²⁹HOWE, ALEXANDER C, and SCHMIDT, JAMES M The treatment of bronchomycosis with x-ray, N Y St Jr Med, 1925, xxv, 60

ADDITIONAL REFERENCES

- BIANCHI, A E, and NINO, F Sobre un caso de blastomycosis pulmonar por "monil" n sp Bol Inst de clin quir, 1928, iv, 531
- CASTA, ARIANO R, and LORENZO, RAMON Contribucion al estudio de las broncomicosis, Rev Soc Med Int, 1925, i, 593
- CHALMERS, A J, and MACDONALD, N Bronchomoniliasis in the Anglo-Egyptian Sudan and Egypt, Jr Trop Med and Hyg, 1920, xxiii, 1
- DRSMIDT, F P G Type of monilia in a case of suspected pulmonary tuberculosis in a European, Kenya and E African Med Jr, 1927, iii, 272
- GILBERT, RUTH, and GROFSBECK, WILLIAM M A study of monilia isolated from sputum Am Jr Pub Health, 1930, xx, 1
- GOMES J M Mycose broncho-pulmonar *Monilia butantancensis*, Annaes Paulistas de Med e Cir 1924, xv, 246
- JACOBO I Notes on some cases of Castellani's bronchomoniliasis, Jr Trop Med and Hyg, 1920, xxiii, 250
- JONES, TR, and SIMPSON, R H Bronchomoniliasis, Lancet, 1923, ccv, 108,
- JOHNS FOSTER M Five cases of pneumonia in which *Monilia pulmonalis* was demonstrated in the fresh sputum New Orleans Med and Surg Jr, 1924, lxxvii, 8
- MACEO, J W, S, and INGRAM, A Bronchomoniliasis complicating pulmonary tuberculosis in a native of the Gold Coast West Africa Ann Trop Med 1926, xv, 51
- MASON, GILBERT PEARCE W Tropical bronchopulmonary mycosis, Jr Am Med Assoc, 1921, lxxvii, 110, Id Pulmonary tuberculosis, pulmonary mycosis and pulmonary spirochetosis, Mil Surg, 1921, xlix, 81
- PANTIN, M Bronchomoniliasis in China, China Med Jr, 1918, xxxii, 318
- PARK, WILLIAM HALLOCK, and WILLIAMS, ANNA WESSELS Pathogenic microorganisms, Philadelphia, Lea and Febiger, 8th ed, 1924
- PARMANAND, N J Notes on a case of bronchomoniliasis, Indian Med Gaz, 1922, lvii, 418
- REDANELLI, P Experimental moniliasis, Jr Trop Med and Hyg, 1924, xxviii, 211
- SARTORY, A, and MOINSON, L Sur un cas de moniliasse bronchique, Compt rend de l'Acad des Sciences, 1922, clxxiv, 77
- SHAW, FREDERICK W A monilia from the respiratory tract, Jr Lab and Clin Med, 1927, xii, 968
- SIMON, CHARLES E A case of yeast (monilia) infection of the lung, Am Jr Med Sci, 1917, cliii, 231
- STOKES, WILLIAM ROYAL, KISIR, EDGAR F, and SMITH, WILLIAM H Bronchomycosis, Jr Am Med Assoc, 1930, xcvi, 14
- SUR, TARAKNATH Bronchomoniliasis, Indian Med Gaz, 1921, lvi, 445
- TALICI, R V, and MACKINNON, J F Estudio de algunas monilias de los espantos, Bol Inst de clin quir, 1928, iv, 502
- WALLACE, G I, and TANNER, F W Etiological agent in bronchomycosis Am Rev Tuberc, 1927, xv, 373

Post-Vaccination Encephalitis*

By CHARLES ARMSTRONG *Surgeon, U S Public Health Service,
Washington, D C*

POST-VACCINATION encephalitis is a disease of unknown etiology that has appeared in recent years and which occurs without regard to the existence of known factors other than the presence of a recent vaccination against smallpox. The disease has a mortality rate of approximately 43 per cent and has associated with it pathological changes of the central nervous system which are similar to those found in the acute nervous manifestations occasionally noted following smallpox, chicken pox, measles and certain other acute infections.

HISTORY AND EPIDEMIOLOGY

Lucksch⁴ in June, 1924, published a series of three cases with post-vaccination nervous manifestations which occurred in Czechoslovakia. Following this publication, some 600 such cases have been reported from Europe—Holland, England, Germany and Norway, in the order named, having suffered the greatest number of cases. A number of additional European countries have had a few cases. Outside of Europe reported cases appear to be mainly confined to the United States.

An isolated case or two has been reported from both Asia and Africa while Australia, South America, Central America, Mexico and Canada have not reported instances of this complication, notwithstanding the fact that, during the last few years, authorities in these countries have been on the alert for them. In the United States 51 proven or probable cases have been recorded for the ten year period just prior to 1931. Forty-one of these occurred during the last three years of this period, or a rough estimate of one case for each 350,000 vaccine points sold in the United States during 1928, 1929, and 1930.

Not only has post-vaccination encephalitis when judged on the basis of reported cases, shown a tendency toward unequal international distribution but within the various heavily involved countries it has shown a tendency to greater prevalence in certain localities than in others. This peculiar localization of cases seems scarcely to be explained by the relative number of vaccinations performed in the different localities or by differences in the methods of vaccination which were employed. Nor have the cases followed the employment of any particular vaccine virus. A striking number of instances have also been reported in

*Presented at the Baltimore Meeting of the American College of Physicians March 24, 1931

which two cases have developed in the same family

The heaviest incidence encountered in the United States occurred in a city of approximately 450,000 inhabitants, where among some 5,000 primary school vaccinations there were five cases, vaccinated within a period of thirteen days, which developed post-vaccination encephalitis. These cases were vaccinated by five different vaccinators who employed various types of single insertions. The same manufacturer's vaccine was used in each of the five cases. This fact, however, loses significance since this producer sold most of the vaccine virus used in the locality referred to during the fall of 1930. The same producer, moreover distributed vaccine virus to many localities of the United States without similar group incidence having been noted elsewhere. Moreover, cases are known to have followed the use elsewhere of vaccine prepared by several different manufacturers. In the affected areas of Europe cases have followed the use of rabbit brain virus, as well as calf strains from many sources including virus imported ready to use from countries in which post-vaccination encephalitis had not been reported.

The complication occurs usually but not invariably following the first or primary "take" and is, therefore, largely confined to children. Adults are, however, occasionally attacked. In affected countries where infant vaccination is practiced to a considerable extent a relative rarity of this complication has been noted following vaccinations performed during the

first year of life, the incidence being estimated by Scott⁵ as about one-sixth of that observed following primary vaccinations performed at later ages. However, if the comparison were made between primary vaccinations under one year and those performed at school age the figure would be probably even more favorable to infant vaccination. In the United States the cases so far reported range from 3 to 49 years in age. Both males and females are susceptible. The complication may develop from a few days to several weeks following the vaccination but there is a striking tendency for it to make its appearance from the tenth to thirteenth day inclusive following primary vaccinations, with a tendency for the interval to be somewhat shortened in cases which follow secondary vaccinations. In other words post-vaccination encephalitis when it develops usually appears when the vaccination is at its height.

European cases have usually followed multiple insertion vaccinations, this, until recently, being the approved method of vaccination in the affected countries. In some instances the complication has followed local "takes" of exceptional severity and in at least one instance was accompanied by a synchronously appearing generalized eruption interpreted as generalized vaccinia.

European cases have, however, appeared following single insertion vaccinations and in the United States all the cases have followed this type of insertion. The evidence, moreover, is clear that in many instances the local "takes" ran a satisfactory course and

were not of exceptional severity

CLINICAL PICTURE

The onset in post-vaccination encephalitis is usually sudden with a feeling of illness, fever, vomiting and headache. Drowsiness and coma may supervene rapidly.

The neurological symptoms vary markedly in individual cases and may point to a major involvement of the meninges, the brain, the brain stem or the cord. Depending upon the regions involved several types of the disease have been recognized by those who have studied particularly the clinical manifestations.

1 *Meningeal Type* This type is common in infant cases, is marked by vomiting, headache, rigidity and retraction of the neck and often by convulsions. The Kernig and Brudzinski signs may be positive and a meningiticcy may be present.

2 *The Cortical Type* In this type convulsions are the most prominent symptom. In two cases of our series convulsions appeared suddenly after the children who were considered to be quite well had been put to bed for the night. Both tonic and clonic convulsions may occur in the same individual accompanied by loss of consciousness. Disturbances of sight and hearing may be present. Such attacks may be rapidly fatal, death in one of the cases investigated resulted within twenty-four hours from the onset of symptoms which made their appearance eight days following the vaccination. In one non-fatal case of this type there is marked mental deterioration with attacks of petit mal apparent after a period of two years. In another case attacks of petit mal are

still appearing six months after the subsidence of acute symptoms.

3 *Brain Stem Type* In this type somnolence, rigidity, tremors, twitching, with altered reflexes, are usual features. The eye muscles usually escape but may show involvement in some cases.

4 *The Myelitic Form* Here the involvement of the lower motor tracts may produce a picture simulating that of poliomyelitis with crippling of one or more extremities. However cases showing a complete paralysis of the lower limbs, such as would almost surely give a bad prognosis for prompt recovery of function in poliomyelitis, may clear up dramatically within a few days. In other instances the myelitic form may present the picture of a transverse myelitis with loss of motion and sensation below the involved segments. In one case of this type which we have observed there is still complete loss of motion and of sensation below the affected segment after a period of six months. Cases of this type have, however, been reported in which recovery has taken place more or less promptly.

5 *Tetanic Form* A tetanic type with trismus and opisthotonus as prominent symptoms has been occasionally noted both in this country and in Europe. Such cases are of especial interest in that they may be confused with post-vaccination tetanus. The clinical picture in these cases, however, has as a rule been rather atypical for tetanus.

While these five clinical types of post-vaccination encephalitis have been recognized among pathologically confirmed cases and are of assistance in

the clinical understanding of the disease, it should be remembered that the classification is an arbitrary one and that most cases present symptoms suggesting two or more of these clinical groups. For instance, headache, drowsiness or coma, rigidity of the neck, convulsions—often of Jacksonian type, incontinence or retention of urine, altered reflexes and paresis or paralysis are features which may be met in cases which differ markedly in other respects. Sensory disturbances have been most frequently noted in the lower extremities. Loss of hearing and sight have been noted in a few instances. It is to be noted that alertness is sometimes encountered in place of the usual lethargy and pains may be prominent symptoms. Trophic disturbances have been occasionally met with.

DIFFERENTIAL DIAGNOSIS

Cases have been mistaken for meningitis of epidemic or tuberculous type, meningismus, encephalitis lethargica, poliomyelitis, sunstroke, cerebral hemorrhage, tetanus, epilepsy, and hysteria. In central nervous disorders the patient should always be examined for the presence of a recent vaccination "take." The presence of a vaccination performed within 30 days of the onset of nervous symptoms should suggest the possibility of post-vaccination encephalitis. In case the onset falls between the tenth and thirteenth days inclusive, this fact is of equal, if not indeed of greater importance, in making a diagnosis of post-vaccination encephalitis than is the character of the nervous symptoms themselves, when the differential diagnosis lies between post-vaccine

tion encephalitis and post-vaccination tetanus. An interval of 14 days or less from vaccination to onset of symptoms strongly favors post-vaccination encephalitis, while one of 17 to 24 days or longer strongly favors post-vaccination tetanus. The spinal fluid in post-vaccination encephalitis is clear, shows no visible or cultivatable organisms, and may be essentially normal. However, it is usually under increased pressure with an augmented cell count. In a few instances vaccine virus has been demonstrated in the cerebro-spinal fluid but this has been an exceptional finding.

PATHOLOGY

The central nervous system changes encountered in post-vaccination encephalitis are distinct from those of poliomyelitis or of encephalitis lethargica, but are similar to those encountered in the nervous system involvement which occasionally follows acute infections other than vaccinia. The characteristic finding in these cases consists of adventitial and periaventitial round cell infiltration mainly confined to, but distributed throughout the white matter of the brain and cord. With the Weigert or other appropriate staining method zones of myelin degeneration may be seen centered about the smaller vessels and gradually fading into normal myelin tissue. These perivascular lesions usually, though not always, have shown a symmetrical distribution. Their number and intensity may, however, vary at different levels, a fact which accounts for the variability of symptoms.

PROGNOSIS

Among the cases so far reported 13 from each hundred have ended

fatally In non-fatal cases the recovery is usually prompt and without sequelae Exceptions to this rule are, however, far from rare

PREVENTION

Beyond the fact that vaccinations performed during the first year of life are relatively less liable to be followed by post-vaccination encephalitis than are primary vaccinations performed later, little is known as to prevention

The Rolleston Commission in Great Britain recommends the abandonment of multiple insertions in favor of a single small implantation of virus and is experimenting with dilutions of lymph While such measures aimed toward a milder type of local and general vaccination response would seem to be indicated, their value in the prevention of the complication under discussion has yet to be established

TREATMENT

In addition to symptomatic treatment great care should be taken to pre-

vent the development of bed sores, or of cystitis in cases requiring catheterization Horder,³ Hekman,² and Gruneberg¹ have utilized the serum from vaccinated individuals, preferably those recently vaccinated, in the treatment of fourteen cases of post-vaccinal encephalitis and consider their results as encouraging The same treatment has been employed in a few cases in this country but without any clear indication as to its value

ETIOLOGY

While a definite relationship between vaccinia and the occurrence of post-vaccination encephalitis has been established, the exact nature of this connection is still obscure Attempts to produce the condition in laboratory animals have in the opinion of most workers met with uniform failure Various hypotheses have been advanced in an effort to explain the occurrence of the condition but time will not permit of their consideration

REFERENCES

- ¹GRUNEBERG Cited from Hekman, 1930
- ²HEKMAN, J L'encephalite postvaccinale et son traitement par le serum homologue, Bull Acad de Méd, 1930, ciii, 539-551
- ³HORDER, T Case of cerebral symptoms following vaccination, rapid recovery after intrathecal injection of post-vaccinal serum, Lancet 1929, vi 1301
- ⁴LUCKSCH, F Vaccination and encephalitis, Med Klin, 1924, vii, 1170-1171
- ⁵SCOTT, T F M Post-vaccinal encephalitis in infancy, Brit Jr Child Dis, 1930, viii, 245-269

Clinical Aspects of Portal Cirrhosis*†

By ALBERT M. SNELL, M.D., F.A.C.P., Rochester, Minnesota

STUDIES on the experimental pathology of the liver have thrown light on many obscure clinical features of portal cirrhosis, and have shown the significance of certain points concerning the genesis and course of the disease which are not generally appreciated. The fact that ascites can be produced only occasionally in animals, and then only with difficulty, and after much injury has been done to the liver, suggests that in man the clinical syndrome of portal cirrhosis with ascites must represent the terminal stage of a long-lasting disease. Just as the general well-being of animals which are receiving daily sublethal doses of hepatic poisons persists until the amount of functioning hepatic tissue is reduced to a critical point, so does the human victim of cirrhosis frequently remain unaware of the presence of the disease until irreparable injury has been done.

The hepatic lesions which are included under the generic term of hepatic cirrhosis are supposed to represent the end-result of a process of repair and progressive fibrosis consequent on successive focal degeneration

or necrosis of the hepatic cells at the periphery of the lobules.⁴² The reparative processes eventually restrict the portal, venous and capillary bed, and the anatomic end-result is disorganization of hepatic structure with lobulation and formation of adenomas. The physiologic end-results are two: portal hypertension and hepatic insufficiency.

Theoretically any toxic substance which is capable of destroying or injuring hepatic cells, and which may act intermittently over a long period of time, is capable of producing the anatomic lesions of cirrhosis. Whereas a number of factors probably enter into the production of the disease, the end-result is apparently not specific for any particular agent. So far as can be seen now, it appears that the various forms of cirrhosis resulting from diffuse infectious processes such as syphilis, the use of alcohol, or of several other chemical poisons, are much alike clinically and even pathologically. It is for this reason that a clinical classification of cirrhosis is so hard to make. Many clinical types have been described, some of which are reasonably well defined. Among these may be mentioned: (1) portal cirrhosis with either hypertrophy or atrophy of the liver, (2) biliary cirrhosis, either primary or secondary to extrahepatic biliary obstruction, (3)

*Read before the American College of Physicians, Baltimore, Maryland, March 25, 1934.

†The author desires to acknowledge the assistance of Dr. J. H. P. in the preparation of this paper.

pigmentary cirrhosis (hemochromatosis), (4) capsular cirrhosis (polyserositis), and (5) the cirrhosis of Wilson's disease. For the purposes of this paper portal cirrhosis may be defined as the end-stage of a degenerative or inflammatory hepatic lesion which has reached the stage of lobulation and which more or less restricts the portal venous circulation.

ETIOLOGY

Experimental cirrhosis has been produced chiefly by toxic substances which enter the liver through the portal blood stream. Biliary cirrhosis secondary to experimental obstruction of the common bile duct may progress to portal obstruction and ascites. Clinically, a similar situation prevails. There are many etiologic agents which are supposed to be capable of causing hepatic injury, but the evidence against most of them is largely circumstantial. Alcohol may be cited as a case in point. Although about fifty per cent of patients with portal cirrhosis admit the use of alcohol, not all of them have been heavy drinkers, and in only about five per cent of patients who exhibit marked evidence of alcoholism do hepatic lesions of any great consequence develop. There is, however, as Rowntree⁴⁴ and others⁴⁵ have shown, some parallelism between the death rate from alcohol and that from hepatic cirrhosis. Functional hepatic injury after abuse of alcohol has been demonstrated by von Bergmann,⁴ by means of tests on the rate of excretion of bilirubin, he has shown, also, that a similar delay in excretion of bilirubin exists in chronic alcoholism and in portal cirrhosis.

Although alcohol will not produce entirely satisfactory experimental cirrhosis, hepatic necrosis and fibrosis may follow its prolonged administration.¹⁵ It seems well established that it is capable of producing structural hepatic injury, but whether it acts directly or through some intermediary product is unknown. It is known to produce changes in the gastro-intestinal tract which may in themselves be the source of toxic substances, or it may permit absorption of the latter from the intestine. It is also recognized that alcohol may act as a solvent for toxic organic substances of intestinal origin. Obviously not all cirrhosis is of alcoholic origin. In India, alcoholism is rare but cirrhosis is common.⁴³ Yang,⁵² in reporting eighty-four cases of cirrhosis in Chinese, found that alcohol could be a factor in only two cases.

The relation between cirrhosis and syphilis is also debatable. The typical result of syphilitic inflammation in the liver is the so-called *hepar lobatum*, but diffuse syphilitic hepatitis may produce a cirrhotic process indistinguishable from the alcoholic type.²⁷ LeDuc²⁷ claimed that seventy-five per cent of patients with cirrhosis have microscopic evidence of syphilis elsewhere in the body. Experience at The Mayo Clinic has shown that one-fourth of the patients in the ascitic stage of cirrhosis have had either a positive Wassermann reaction or a more or less definite history of syphilis. Of nine of the patients who came to necropsy with cirrhosis and serologic evidence of syphilis, only one had typical *hepar lobatum*, the remainder presented the usual picture of

atrophic cirrhosis I have therefore included in this study cases of portal cirrhosis in which syphilis may have been a cause, but in which the symptoms did not disappear under specific treatment.

In my experience, cholecystitis and infection of the biliary tract are frequently associated with cirrhosis, but the evidence is not sufficiently complete to differentiate cause and effect. Koster²⁶ and his associates have described early fibrotic changes in the periportal tissues of patients with chronic cholecystitis, and expressed the belief that these changes were secondary to cholelithic disease, and that the spread of infection was by way of lymphatic channels. Other types of gastro-intestinal disease may enter into the genesis of cirrhosis. As Opie³⁰ has suggested, a combination of bacterial infection and chemical intoxication may be involved. The liver may also be injured more or less severely by many of the infectious diseases. In Yang's³² series, fifty patients gave histories of bacillary dysentery or typhoid fever, a previous history of typhoid fever is not uncommon in cases of cirrhosis studied at The Mayo Clinic. Other possible etiologic factors are inorganic arsenical poisoning,³³ hyperthyroidism, toxemia of pregnancy, chronic intoxication³⁴ from protein and malaria.

Certain observations on the experimental aspects of cirrhosis must be considered in a study of the etiology of the condition in man. Research workers agree that when they stop giving the drug which is destructive to the liver the liver of the animal returns to its approximately normal state pro-

vided the lesion is not too far advanced. From this one must infer that in man the poisons which produce cirrhosis must operate continuously over a long period of time. Experimentally there is also marked individual variation in the response of the liver to chemical injury. As Bollman and Mann⁸ have suggested, the response may be due to the state of the liver at the time the toxic agent acts, or it may bear some relationship to the hepatic reserve of glycogen present in the organ at the time.

An obscure point in the pathogenesis of cirrhosis is the nature of the overgrowth of connective tissue which follows some forms of hepatic injury, and which is absent in others. The stimulus to formation of connective tissue apparently must be an essential element in the etiology of portal cirrhosis. It is also recognized that previous hepatic injury leaves the liver with a variable amount of regenerated hepatic tissue, which has been shown to be unusually susceptible to injury. In other words, successive degenerative lesions of the hepatic parenchyma are more and more easily produced, and each in turn interferes further with the hepatic blood supply. The ability of experimentally produced anoxemia^{31, 35} to cause degenerative changes in the hepatic cells must also be considered. Recent studies by Rich³¹ show that anoxemia may operate as a cause of depressed hepatic function, from these studies it is apparent that the hepatic arterial blood flow may be of great importance in determining the course and progression of any hepatic lesion.

CLINICAL STAGES OF CIRRHOSIS

It is clearly established that, in both animals and man, portal cirrhosis may be present without ascites or, in fact, without any marked symptoms of visceral disease. This may be attributed to the enormous physiologic reserve of the liver, to its remarkable regenerative properties, and to the collateral circulation which accompanies the sclerosing types of hepatic lesions. The course of cirrhosis may therefore be divided into two stages, one a preascitic stage, and the other an ascitic stage, or, as Rowntree⁹ has stated, an hepatic lesion may exist either with a compensated or a decompensated portal circulation. The relative frequency of the two stages of the disease is not definitely known, but it has been said that ascites develops in from fifty to eighty-five per cent of cases of cirrhosis. The compensated, or preascitic, stage of the disease has attracted little attention, the attention of physicians has remained focused on the end-stage of the disease. More complete knowledge of the nature and duration of the preascitic stage is now highly desirable. I have, therefore, attempted to review the cases of portal cirrhosis seen at The Mayo Clinic from 1924 to 1929 inclusive with the idea of learning something about the clinical course, the symptoms of the earlier stages, the criteria on which a prognosis can be based, and the rationale of medical and surgical treatment.

The material to be studied comprises 399 cases divided into three groups. (1) 135 cases in which nodular cirrhosis of the liver was discovered in the course of surgical operations for other abdominal lesions,

(2) 152 cases in which a clinical diagnosis of portal cirrhosis in the preascitic stage was made, and (3) 112 cases of cirrhosis in the terminal or ascitic stage. Some idea of the incidence of cirrhosis among patients in the clinic may be gained from the fact that, in the period of six years covered by this study, 399 patients were found to have the disease in a total of approximately 400,000.

Cirrhosis Discovered at Operation

In the group of 135 cases, in which the disease was discovered at operation, hepatic lesions were suspected in only a few, and then because the spleen had been found to be enlarged. I have excluded from this group patients with obstructive lesions of the common bile duct, and those whose hepatic lesions were more localized than diffuse. In some of this group biopsy of the liver was obtained, but in most instances the diagnosis was made from the gross appearance of the liver only. It is probable that some cases were overlooked, since the liver may appear grossly normal and yet contain the microscopic lesions of portal cirrhosis. It is also probable that there were some positive errors of diagnosis, but in general the surgeon's opinion may be regarded as reliable.

The observations at operations in which cirrhosis was found accidentally are given in figure 1. The number of cirrhotic livers discovered at operation on the gallbladder is not large considering that approximately 7000 operations were done on the biliary tract in this period. The discovery of cirrhosis at this type of operation may perhaps be explained on the basis of the proximity of the liver and the

extrahepatic biliary tracts. However, many experienced surgeons feel that lesions of the gallbladder, of long standing may lead to a cirrhotic process in the liver, at least it is agreed that the two conditions are not infrequently associated. This view, which rests on clinical impressions only is partially substantiated by the views of Koster²⁶ and his collaborators. There is, of course, a possibility that the disease of the liver may have been primary, and that of the gallbladder, secondary.

That cirrhosis was found in the course of approximately twenty operations which were done for peptic ulcer was somewhat surprising. It may be that these ulcers were secondary to the hepatic lesion present, since Bollman⁷ has found that in experimental obstructive jaundice, typical callous ulcers of the duodenum are commonly found. Beig and Jobling³

have also advanced the view that hepatic lesions may favor the formation of peptic ulcers.

The cirrhosis which accompanies Banti's disease needs no further comment. Johnston's²³ recent paper contains a summary of the current views on the subject. Thirteen of the patients with Banti's splenomegaly had cirrhosis of marked degree, with reduction of about fifty per cent in the size of the liver. Hepatic functional tests were made in a number of these cases and only moderate retention encountered. Excluding the group with Banti's disease, only eight of the 135 patients had definite splenic enlargement, and in only a few was there any mention of the collateral circulation. From this fact it would appear that in primary portal cirrhosis an enlarged spleen occurs late, when the portal circulation is greatly restricted and that interference with flow of

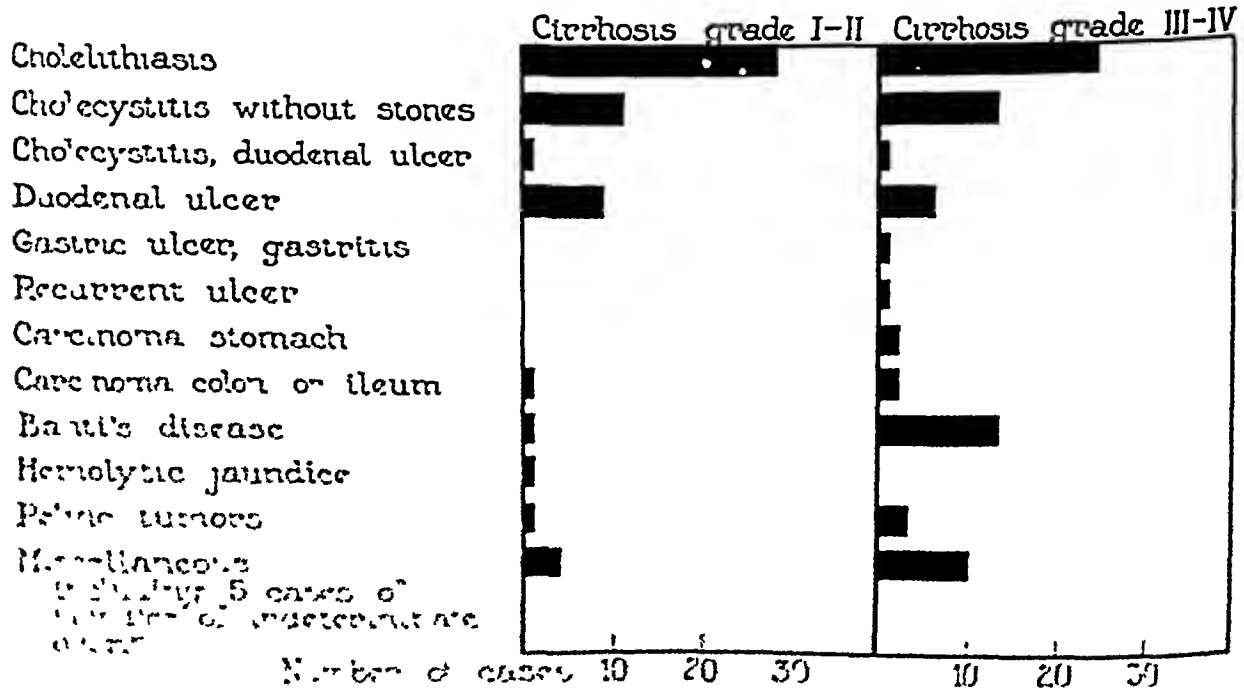


FIGURE 1. Comparison of conditions associated with cirrhosis in two groups of patients.

portal blood must exist for some time before collateral channels are established

The symptoms which brought these patients to operation are of some interest. Thirty had typical gallbladder colic, twenty-eight had pain in the upper part of the abdomen, and soreness associated with some indigestion, eighteen complained of poorly localized or bizarre abdominal pain, seventeen had the typical syndrome of peptic ulcer, and ten of these seventeen gave histories of hematemesis and melena. Gastro-intestinal bleeding, without other symptoms, was noted in nine cases. Nine patients gave histories of jaundice. In reviewing these histories, it is difficult to see how hepatic disease could have been suspected in more than a small percentage of the cases. The routine inquiries as to alcoholism and syphilis gave little, if any, information of value since only nine of the patients admitted the abuse of alcohol and only six gave histories of syphilis.

The outcome of the disease in this group of cases is of considerable interest. Nine patients subsequently had ascites, twenty-four have died, and in at least fourteen the hepatic lesion found at operation apparently was responsible for death. The immediate surgical mortality in the 135 cases was not high, so that the subsequent death of the patients may perhaps be attributed to the progress of the disease in the liver. Of the patients with Banti's disease only two have died and the death of one could not be attributed to hepatic disease.

Many of the surviving patients have written to complain of indefinite gaseous dyspepsia, weakness or gas-

tro-intestinal bleeding. On the other hand, a large group have replied to letters of inquiry with the statement that they were perfectly well. The subsequent health of a number of the patients with livers described by the surgeon as being markedly atrophic or "hobnail" in appearance, has remained good and they have experienced no inconvenience. In many of these cases it is hard to see how the operation could have had any effect on the course of the cirrhotic process, but in some the formation of postoperative adhesions may have helped to establish collateral circulation, which in turn may have deferred the development of ascites. In some the removal of diseased gallbladders may have had beneficial effect.

Preascitic Portal Cirrhosis Diagnosed Clinically. In the group of 152 cases in which a clinical diagnosis of portal cirrhosis was made in the preascitic stage, confirmation was not obtained by operation or necropsy. A large percentage of these diagnoses were made because a history of alcoholism or syphilis was associated with the finding of a large liver or spleen and definite retention of dye. The accuracy of diagnosis may of course be questioned, and no doubt some of the patients were suffering from carcinoma or other serious visceral disease. Diagnostic accuracy in the early stages of cirrhosis is disappointingly low and positive criteria have not as yet been established. Often the few symptoms that present themselves are not pathognomonic and the diagnosis must frequently rest on objective evidence.

In the series of 152 cases the most common complaints were of vague abdominal pain, gaseous indigestion, weakness and intermittent jaundice, which was usually painless or almost painless. An enlarged, firm liver was noted in the majority of the cases, and a palpable spleen was commonly found. Edema and signs of collateral circulation were uncommon. In this stage of the disease there was usually only moderate retention (graded 1 or 2) of phenoltetrachlorophthalein or bromsulphalein. More delicate functional tests^{1,19} might have revealed more striking changes.

Seventy-two of the 152 patients are known to be dead, fifty-eight cannot be traced, and only fourteen are known definitely to be living after periods of observation averaging about four years in length. A follow-up study of this group is now being carried out, so that the details presented here are necessarily incomplete. Ascites is known to have developed in nine of the cases.

A few other patients who had a small amount of fluid at the time of examination appear to have recovered completely. One patient in whose case the diagnosis of syphilitic hepatitis was considered, but not proved, regained health under the use of iodides. Another patient with a large liver and marked retention of dye was reported as being well a year after examination. Two patients appear to have died suddenly from gastro-intestinal hemorrhage, and several have died in coma. The high mortality in the group gives striking evidence of the gravity of the disease even in the early stage of cirrhosis.

On the basis of experimental evidence, it seems probable that in the earlier stages of cirrhosis the liver should be able to regenerate, and to become fairly normal, provided the cause of the disease could be recognized and removed. That this actually happens at times is shown by the cases, which are not infrequently reported, in which a man who has been a heavy drinker, and who has begun to show signs of cirrhosis, stops drinking, gets well, and stays well. When etiologic agents continue to act, however, as they apparently do in a majority of cases, the pathologic process continues unchecked, and a fatal termination is the rule.

Cirrhosis with Ascites The appearance of free fluid in the abdomen, which has been characterized as indicative of decompensation of the portal circulation, appears to mark a critical point in the course of the disease. All of the 112 patients of this group had ascites already at the time of registration at the clinic and presented typical examples of the ascitic stage of portal cirrhosis. From all of the cases in the group other causes of ascites could be definitely excluded, in addition, the diagnosis was confirmed in half of the cases by surgical exploration or necropsy. Eighty-two of the patients were males and forty were females; sixty per cent were between the ages of forty and sixty years.

A careful inquiry was made into the early symptoms noted in each case and the results are presented in figure 2. It is significant that approximately sixty per cent of the patients had suffered from various gastro-intestinal symptoms for from two weeks

to twenty years prior to the development of ascites. The average duration of these symptoms was considerably more than a year. Loss of strength was common, but loss of weight does not seem to have been conspicuous until shortly before the appearance of ascites. As in the group without ascites about a fourth of the patients gave histories of slight, intermittent, painless jaundice, often associated with diarrhea, vomiting, and abdominal cramps. Hematemesis was noted as an early symptom in less than ten per cent of cases. Ascites developed suddenly in about eighteen per cent. In six cases, an enlarged liver or spleen had been found or a definite surgical diagnosis of cirrhosis had been made from two to ten years before the development of ascites.

The early symptoms were in contrast to those which were complained of at the time the patient registered at the clinic. After the appearance of ascites loss of strength and weight

were much more striking and abdominal pain or distress was complained of by about half of the patients. Jaundice was present in thirty-eight instances. Gastro-intestinal bleeding was twice as common as in the early stages of the disease.

The physical evidences of the decompensated stage of hepatic cirrhosis are too well known to require particular comment. The combination of characteristic "hepatic" facies, slight jaundice, ascites, edema, and visible collateral circulation, constitutes a picture familiar to all clinicians. Certain incidental features are not so well known. Forty-seven of the patients with ascites had one or more hernias, five had two, and one patient had three. This high incidence is surprising when one considers that in other types of ascites or abdominal enlargement hernia is less frequently encountered.

About fifty per cent of the 112 patients of this subgroup had more or

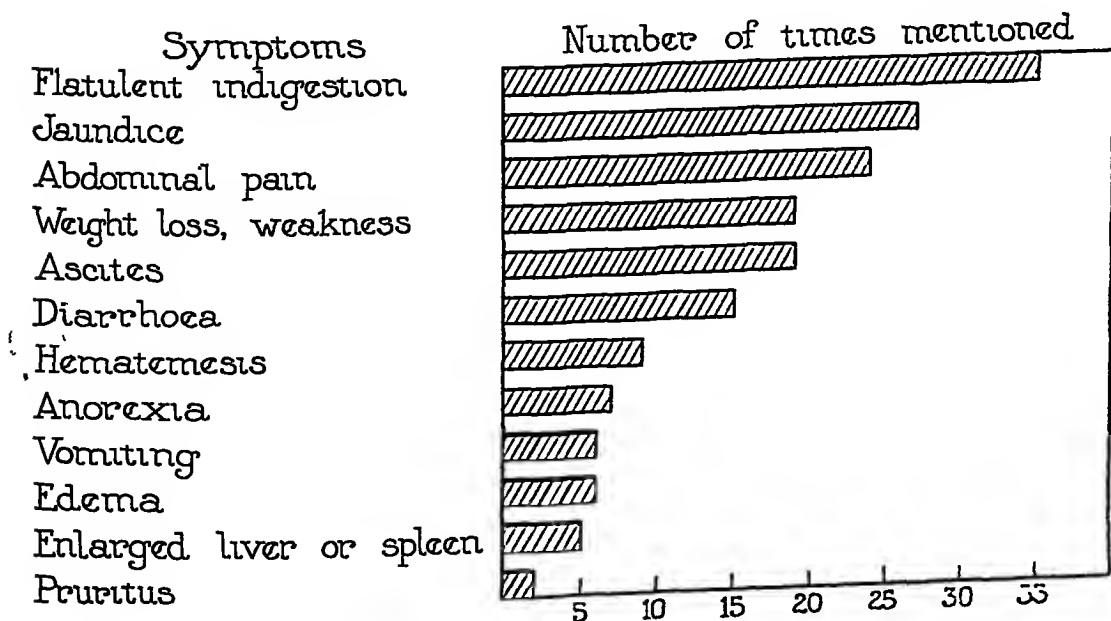


FIG 2 Early symptoms of portal cirrhosis in cases in which ascites develop

less marked collateral venous circulation over the abdomen, lower part of the thorax, or lumbar region. In one case, the size of the peri-umbilical veins was striking, in another, a very large vein was noted over the thorax, and appeared to terminate in the axilla (figure 3)

A palpable liver was noted in sixty per cent of the 112 cases. The degree of enlargement varied greatly at different times in individual cases, and in some cases the size appeared to decrease while the patient was under observation. The spleen was palpable in about forty per cent of the cases. From a consideration of data obtained at operation and at necropsy in this group however, it would appear that clinical conceptions of the size of the liver and spleen may not be accurate, particularly when ascites is present.

LABORATORY TESTS

The laboratory studies require only brief mention. What is to be said about them applies to the series of 112

cases with ascites. Scanty and highly concentrated urine was the rule. Examination of the urine for urobilin and urobilinogen gave variable results which seemed to depend on the presence or absence of slight jaundice. About twenty-five per cent of the patients had slightly elevated values for serum bilirubin at some time while they were under observation. Deep jaundice, however, was rare. In ten cases, the bile acids in the serum were determined by the method of Aldrich,¹⁷ and in all normal values were found.

In about forty per cent of the cases there was a definite anemia, with hemoglobin of fifty per cent or less. The characteristics of the blood in general corresponded to those previously described by King.²⁴ The values for blood sugar and blood urea were normal in practically all cases, although in fifteen of the group the concentration of urea in the blood was elevated at some time in the course of treatment. In one case, and on one occasion only, a very low value for



blood urea (4 mg in each 100 cc) was encountered. In two cases post-operative hypoglycemia was noted. Following the appearance of papers by Minot and Cutler,¹⁴ and Ellsworth,¹¹ determinations of guanidine in the blood were made in a number of cases, but striking or significant changes were not noted.

The tests of hepatic function with bromsulphalein or phenoltetrachlorophthalein proved their dependability in this series of cases, as in other series of cases reported from the clinic.¹⁸ These tests were done in eighty-seven cases, and in eighty, positive results were obtained. The results of repeated tests of hepatic function were remarkably constant in any given case, providing jaundice was not present. In exceptional instances there was reduction in the degree of retention of dye as the patient improved. This was particularly true when the original cause of hepatic injury was discovered and effectively treated.

Tests of hepatic function by means of dyes appear to be influenced by three factors: (1) the amount of blood coming to the liver through the portal vein and the hepatic artery, (2) the presence or absence of jaundice, and (3) the amount of functioning hepatic tissue. The degree of retention of dye seems to indicate, in a general way, the degree of parenchymal injury, although clinically the degree of retention of dye could not be correlated with the size of the liver, the degree of ascites, or the degree of toxemia presented by the patient. The prognostic value of the test, however, appears to be considerable, since patients with retention of dye, graded

three or four, on the average, pursue a much less favorable course than those with low degrees of retention.

CAUSE OF SYMPTOMS OF PORTAL CIRRHOSIS WITH ASCITES

It seems advisable to review briefly what is known of the serious symptoms and signs of portal cirrhosis in the ascitic stage. Pain may be of enteric origin, although other causes cannot be eliminated.²⁸ Jaundice is apparently an expression of hepatic parenchymal degeneration. Hemorrhage appears to be due most frequently to leakage from esophageal varices. These appear to be present in every case of cirrhosis, although they are not always demonstrable at necropsy, since special injection technic may be required to disclose them. In life they have been demonstrated rarely, since esophagoscopy has been performed only infrequently in this group of cases. Gilbert¹⁶ and his associates have performed this procedure in twelve cases, and have found dilated esophageal veins in all. Wolf¹¹ has demonstrated esophageal varices by roentgenologic methods in two cases, and Kiklin and Moersch¹ are reporting a case in which such varices were demonstrated by roentgenologic methods and by esophagoscopy.

The factors which favor bleeding from these varices are not known. Physical exertion seems to precipitate the hemorrhage in some cases. In others, the hasty eating of coarse foods apparently has provoked hemorrhage. A number of patients bled after paracentesis and after operation. Many other patients stated that their

bleeding had begun when they were asleep, a fact that may be explained on the basis of venous stasis and congestion. It is, of course, generally recognized that a hemorrhagic tendency of unknown nature and variable severity exists in hepatic disease of all types, and it is certainly a common accompaniment of portal cirrhosis, although laboratory studies on the coagulating properties of blood in this disease may not always give conclusive proof of the hemorrhagic tendency.

The cause of the ascites has been debated since time immemorial, and a great many possible explanations have been brought forward. Portal obstruction alone is not sufficient, and other factors must be involved. Herick⁹ has expressed the belief that ascites appears when vascular injury has reached such a point that the pressure in the hepatic artery can affect that in the portal system. Feissinger¹² has attributed it to acute degenerative changes and swelling of the hepatic cells, and secondary occlusion of the portal capillaries which are confined in an elastic framework. Bollman⁶ has demonstrated the effect of dietary factors which could hardly operate except through their effect on the hepatic cell or by peritoneal irritation. Occasionally ascites will develop from portal thrombosis. Mann¹¹ has expressed the belief that four factors are involved: (1) interference with portal circulation, (2) lack of absorption from the peritoneal surfaces and from the intestines, (3) peritoneal irritation, and (4) reduction in the osmotic pressure of the tissue fluid. It has been suggested that the ascites is due to an increase in the permeability of the

hepatic cells may interfere with the renal elimination of water.

Little, if anything, is known about the nature of the so-called hepatic coma which is so frequently a terminal event in portal cirrhosis. It is generally agreed that the chemistry of the blood is not altered as it is in the hepatectomized animal, although in occasional cases there is hypoglycemia. Failure of the detoxifying function of the liver has been regarded as significant. Becher² has noted an increase in the amount of phenol and phenol derivatives in the blood of patients with cirrhosis of the liver, which he has attributed to failure of this function.

PROGNOSIS

The prognosis of portal cirrhosis is grave in any stage of the disease. As was previously noted, the mortality in the preascitic stage is high, even in cases in which the disease is discovered accidentally at operation. Of the 112 patients in the group with ascites, eighty-four have died. Coma, gastrointestinal hemorrhages, and intercurrent diseases were the principal predisposing causes of death. Six patients died after operations, and the death of four of them was directly attributable to hemorrhage. Twenty-seven patients died at home from causes unknown to the clinic. The average duration of life of the patients was about sixteen months after the appearance of ascites. The twenty-eight patients who are living have survived on an average about thirty-eight months after the development of ascites. These figures, although not encouraging, are better than the

previously given in the older literature, a point which is demonstrated in figure 4. Formerly the average duration of life after the development of ascites was from two to five months. The longer period of survival of the patients in the group considered in this paper may possibly be attributed to recent improvements in the medical treatment of cirrhosis, but such factors as earlier diagnosis and treatment, a lower incidence of marked alcoholism, and a high degree of intelligent cooperation on the part of many of the patients must also be taken into account. The prognosis is obviously better in the occasional case in which the causes can be found and eradicated.

The prognosis in individual cases can be determined roughly by four

factors: (1) the degree of retention of dye, (2) the response to treatment with diuretics, (3) the general state of nutrition of the patient, and (4) the presence or absence of complicating disease. Patients with low degrees of retention of dye, who respond favorably to administration of diuretics, appear to do particularly well. The same may be said of patients who remain in good nutrition and who are willing to make the necessary adjustments in their manner of living. Complicating diseases, particularly those of an infectious nature, appear to add greatly to the gravity of the situation.

OBSERVATIONS AT NECROPSY

The pathologic changes seen in cases in which patients have died with portal cirrhosis have been described

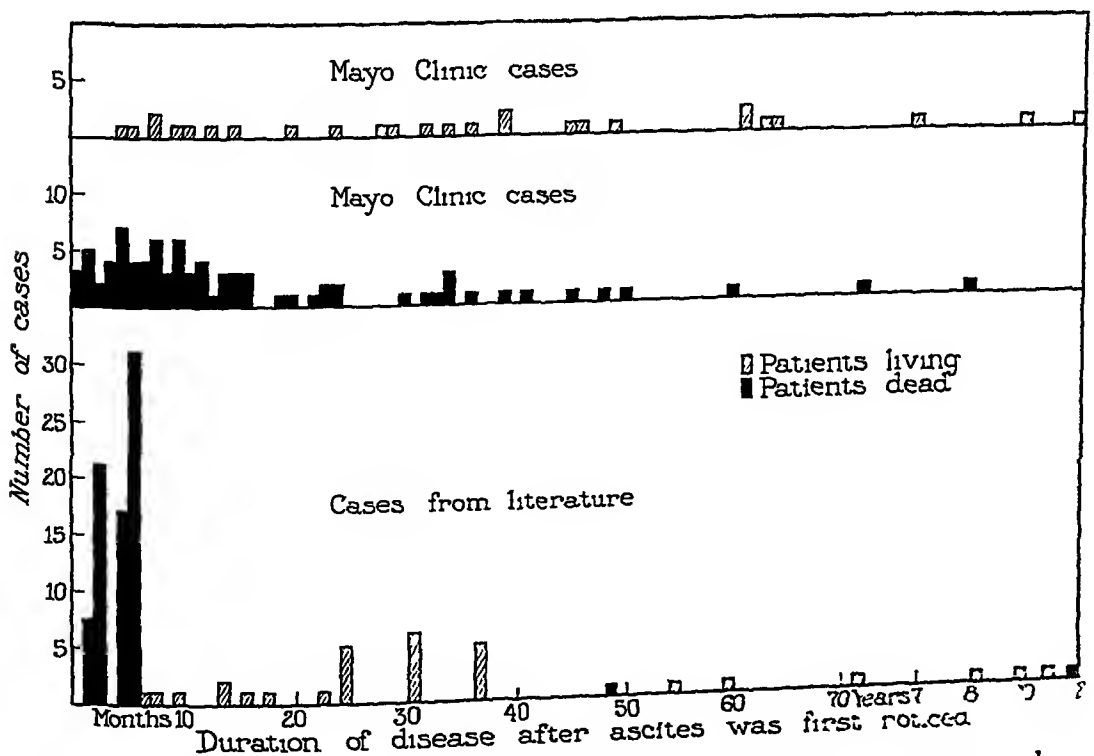
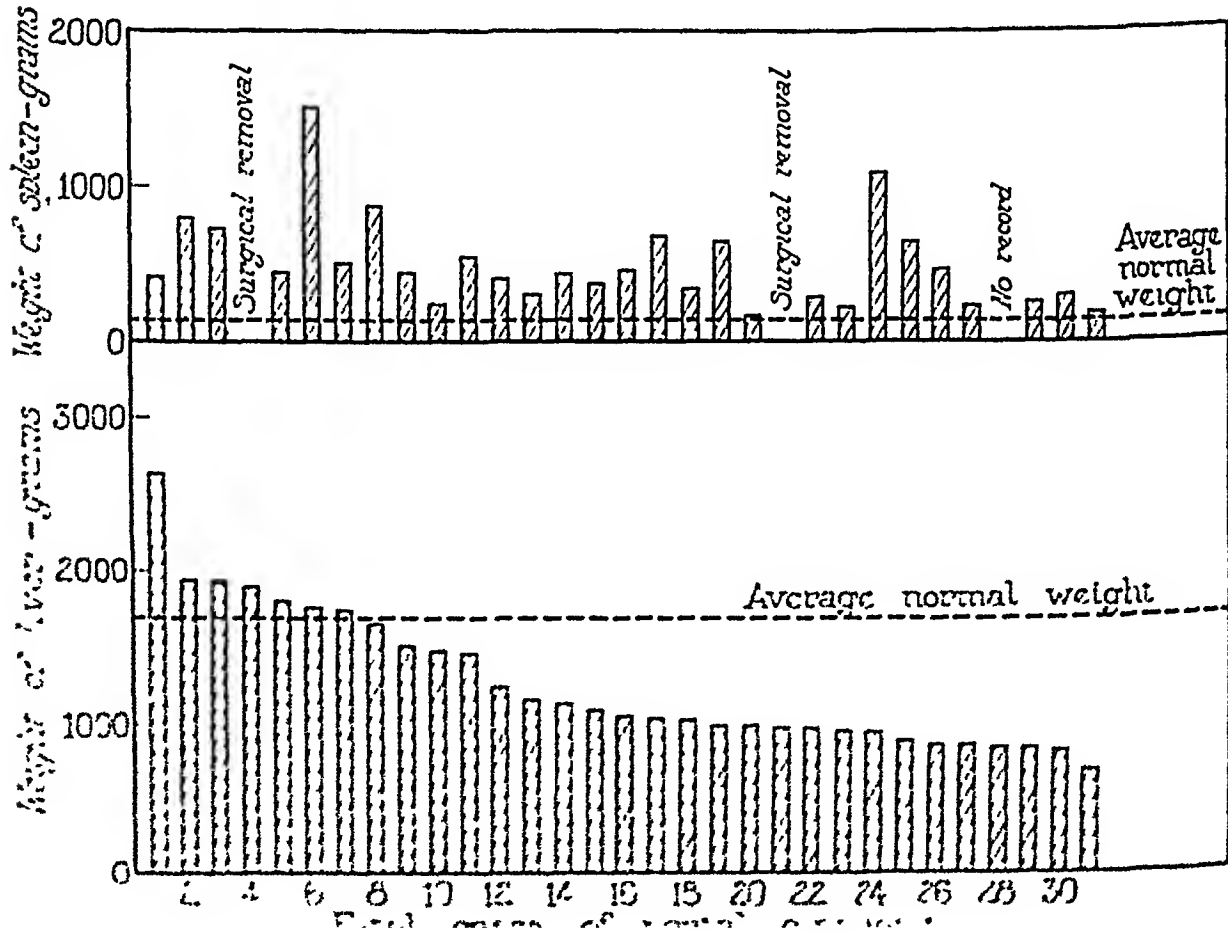


FIG. 4. Average duration of life in portal cirrhosis with ascites: upper two lines—cases seen at The Mayo Clinic, 1924 to 1929 inclusive; lowest line—cases noted in the literature prior to 1921.

often For the sake of completeness, I include here the significant features disclosed in a group of recent postmortem examinations made at the clinic, in the course of the years 1924 to 1930 inclusive A decrease in the size and weight of the liver is fairly uniform in this series, as may be noted in figure 5 The size of the liver does not seem to bear any relationship to the weight of the spleen or to other changes found at necropsy In Nissen's¹⁰ series, reported ten years ago, the average life of the patients was shorter, and the average weight of the liver was considerably higher

Collateral circulation was demonstrable in practically all cases In several, the omentum was adherent to the abdominal wall and represented spon-

taneous omentopexy Esophageal varices were present in every instance, and in at least one-third of the cases there was evidence of recent bleeding into the gastro-intestinal tract In three cases intraperitoneal hemorrhage was noted Edema at various points of the gastro-intestinal tract was common, often associated with congestion and small regions of superficial ulceration Chronic gastric or duodenal ulcers, either healed or active, were present in about twenty per cent of cases Fibrosis of the pancreas was noted in more than one-third of the group Cholelithiasis was found in five cases, chronic cholecystitis without stones was noted in twelve, and marked edema of the gallbladder in two



Active tuberculosis was not found in any case in this group, although healed lesions of tuberculosis were fairly common. Hydrothorax was found in an occasional case and terminal bronchopneumonia was present in about fifteen per cent. Anatomic changes in the kidney were uncommon. This seems significant when it is recalled that many of these patients had failed to respond to diuretics, either at the clinic or elsewhere.

TREATMENT

In the past, the treatment of portal cirrhosis has been directed largely toward removal of ascitic fluid, and there are reasons for believing that the strenuous efforts made in this direction have done much to shorten the life of these patients. It must be admitted, however, that many patients are sufficiently improved by removal of fluid to make the therapeutic attempts along these lines attractive. When one considers the natural course of cirrhosis, and the experimental evidence showing that ascites is an extreme terminal development rather than an essential element of the disease, the possible fallacy of giving ascites first consideration in treatment is obvious. This was noted by Morgagni³⁵ who asks this significant question: "Why should the physician trouble with very strong and violent remedies those in regard to whom he ought to think only how to preserve their lives as long as possible instead of attempting to cure their disorder?"

Treatment in portal cirrhosis should be directed primarily toward the detection and eradication of etiologic

factors, and secondarily, toward the maintenance of the functional integrity of the hepatic cell. It is unnecessary to emphasize the fact that treatment antedating the development of ascites is highly desirable. Success will depend largely on the physician's ability to do these things, and, in the later stages, on the ability of the patient to respond to treatment by diuretics or to surgical measures.

The details of treatment in this group of 112 patients with decompensated portal cirrhosis have been considered elsewhere.⁹ Prior to registration at The Mayo Clinic, treatment of these patients had been confined largely to paracentesis. A few patients had been given diuretics. After registration, eighty-four of the 112 patients were treated with mercurial diuretics combined with ammonium salts in large doses, after the method described by Rowntree, Barrier and Keith.⁴⁵ All of these patients were given a high carbohydrate diet, and water and salt were markedly restricted. About eighty per cent of the patients in this group responded satisfactorily to treatment; in forty-seven per cent the results might be classified as excellent, in about thirty-two per cent they were moderately satisfactory, and in twenty-one per cent they were poor.

Not all patients are suitable for diuretic treatment, and careful selection must be made. Patients with ascites of long standing may be resistant to even the most vigorous treatment, and too much must not be expected of diuretics in the late stages of the disease. In many instances as the disease progresses there is gradual

decline in the effectiveness of diuretics. Elderly and cachectic patients should be treated with caution, if at all. In the presence of marked jaundice, diuretic treatment is rarely effective, and should be employed only with great care. Active gastro-intestinal bleeding and mental symptoms also appear to be contra-indications.

Toxic reactions to treatment do not necessarily preclude further treatment, but they do emphasize the necessity for proceeding cautiously. Feissinger and others¹ have stated that if patients are not improving from the use of diuretics they are probably getting worse, a point which has been substantiated in my experience. Frequent paracentesis does not furnish an adequate substitute for treatment by diuretics. The intervals between tapping become progressively shorter and as White²⁰ has remarked, many patients do not survive even the second paracentesis. The effect of diuretics seems to be more permanent, for reasons which are unexplained. Saxl¹⁸ and Feissinger¹ expressed the belief that in selected cases mercurial preparations stimulate hepatic regeneration and improve hepatic function. The best protective measure in the presence of hepatic lesions, both experimental and clinical, is the administration of carbohydrate by mouth and by vein. The daily use of glucose intravenously has given excellent results in the treatment of impending hepatic insufficiency, and deserves more general trial. Concentrated solutions of glucose (from 20 to 30 per cent) are particularly useful because of the small amount of fluid introduced. Such solutions may be given

daily, in amounts of from 250 to 500 c.c., without apparent harm or discomfort to the patient, and in some instances they appear to have been life saving. The giving of insulin at the same time does not seem to be an advantage. When diuretics do not act, it is usually advisable to begin the forced administration of glycogen-forming substances and to perform paracentesis as often as necessary, to control the accumulation of fluid.

Operations. Surgical measures in cirrhosis have been designated to relieve the patient of ascites by mechanical means, to establish additional connections between the portal and the general circulation, to reduce the load on an overburdened portal circulation, and finally to eliminate channels of collateral circulation at vulnerable points, such as in the lower part of the esophagus. All of these procedures have given variable results and have not been entirely successful. The experience of surgeons in this field has been well covered by the papers of Hughson,²² Hopfinger,²¹ and W. I. Mayo.¹⁷ The various procedures which have been employed are represented schematically in figure 6. The Talma-Morrison omentopexy, which has been so widely used, is accompanied by high immediate mortality, but it has given some fairly good results. Reisman¹⁹ described two cases in which the patients were apparently cured by this means and some gratifying results have been reported from The Mayo Clinic. Hughson's figures are not encouraging. Hopfinger expressed the thought that not more than one third of patients derive any

benefit from this operation, and this has been the experience of Eliot and Colp¹⁰

Splenectomy, which produces such excellent results in Banti's disease, does not appear to be so effective in portal cirrhosis. The differentiation between Banti's disease and portal cirrhosis is often difficult, and doubtless the two diseases are frequently confused. There appears to be a group of young persons with marked splenomegaly and hematemesis who

are benefited by removal of the spleen, and in them definite portal cirrhosis is frequently found at operation. It will be noted, in figure 5, that the average splenic weight in twenty-eight cases of cirrhosis in which the patients came to necropsy was low, and it is difficult to see how removal of these spleens could have altered greatly the course of the hepatic disease. Splenectomy, of course removes a substantial burden from the portal circulation, but the surgical

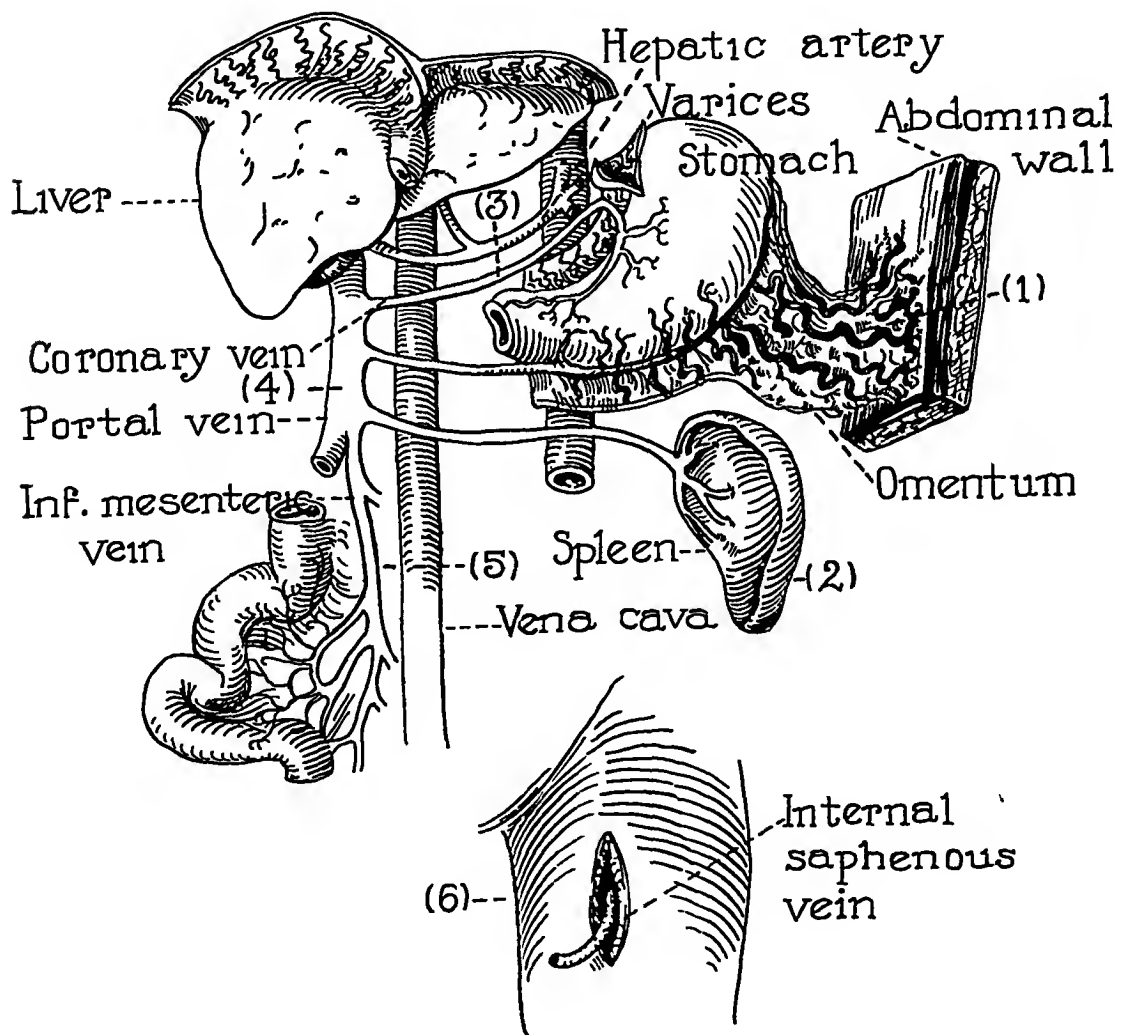


FIG 6 Surgical procedures in portal cirrhosis. (1) Talma-Morrison omentopexy, (2) splenectomy, (3) ligation of coronary veins, (4) Eck fistula, (5) anastomosis of inferior mesenteric vein to vena cava, (6) transplantation of saphenous vein into peritoneal cavity.

risk is considerable and the end-results are not altogether encouraging

Ligation of the coronary veins of the stomach, either alone or in combination with splenectomy or omentopexy, has been done successfully⁴⁶ in a few selected cases, with good results. The operation is primarily directed toward the control of bleeding from esophageal varices and deserves a more extended trial. Various forms of anastomosis between the portal and venous circulation have been advocated, notably the Eck fistula⁴⁹ and anastomosis between the mesenteric vein and the vena cava.⁵ Some good results have been reported, but in many cases sufficient connection between the portal and general circulation exists to render these operations more or less unnecessary. Various mechanical measures also have been proposed to rid the patient of ascites. Of these the most popular seems to be the method of Ruotte,¹⁷ who has transplanted the saphenous vein into the peritoneal cavity. Success has been reported in some cases¹¹ and the operation recently has been advocated again by Franke.¹⁴

Most surgeons who have had large experience with the surgical treatment of portal cirrhosis feel that all types of operative treatment are carried out too late to be of much benefit to the patient. At the present time it is the general practice of physicians to try a variety of remedies before considering surgery. Knowledge of the usual course of cirrhosis makes the advisability of this plan obvious. If patients do not react to diuretics and are progressively failing, it is unlikely that they will experience any relief

from operation. If patients are young, in good condition and respond well to diuretics, omentopexy or splenectomy should be seriously considered. If hematemesis is a prominent feature, ligation of the coronary veins may be carried out with good prospects of relief. Even with the best selection of cases the surgical risk is not to be disregarded, and one must be prepared for many discouraging failures.

SUMMARY

In reviewing a group of approximately 400 patients with portal cirrhosis in all recognizable stages of the disease, the chronicity and latency of the condition before the development of ascites is striking. Of patients with cirrhosis who are seen, the number of those who are in the preascitic stage is perhaps twice as great as the number of those who are in the ascitic stage. In the earlier stages, when these stages can be detected, eradication of causative factors may stop the progress of the disease. This is particularly true when alcoholism, syphilis, cholecystic disease, or chemical poisoning are causes.

The early symptoms are largely those of vague indigestion, intermittent jaundice, or gastro-intestinal bleeding, and in cases in which these complaints are made, tests of hepatic function may reveal the diagnosis. The earlier recognition of cirrhosis is highly to be desired because in the earlier stages, arrest of the process is theoretically possible.

The appearance of ascites marks a critical point and indicates the onset of a lower of ominous portents of significance. Treatment in the

stage has been facilitated by the use of mercurial diuretics, and review of the results obtained in a series of 112 cases with ascites shows longer duration of life than in comparable groups

reported in the literature. The indications for medical and surgical treatment, and the limitations of each, are considered with reference to the known course of the disease.

BIBLIOGRAPHY

- ¹ALTHAUSEN, T L, GUNTHER, L, LAGEN, J B, and KERR, W J. Modification of the dextrose tolerance test as an index of the metabolic activity of the liver, *Arch Int Med*, 1930, xli, 482-493.
- ²BECHER, ERWIN. Über Steigerungen des Blutwertes von Phenol und Phenolderivaten und über das Auftreten von freiem Phenol im Blute bei Leberzirrhose, *München med Wchnsch*, 1930, 1, 751-752.
- ³BERG, B N, and JOBLING, J W. Biliary and hepatic factors in peptic ulcers, an experimental study. *Arch Surg*, 1930, xx, 997-1015.
- ⁴BERGMANN, G. Zur funktionellen Pathologie der Leber insbesondere der Alkohol-Ätiologie der Cirrhose, *Klin Wchnsch*, 1927, vi, 776-780.
- ⁵BOGORAZ, N A. La transplantation de la veine mesenterique superieure dans la veine cava inferieure, *Med russe*, 1913, 11.
- ⁶BOLLMAN, J L. Experimental cirrhosis of the liver, *Proc Inter-state Post-Grad Med Assemb N Amer*, 1928, 387-390.
- ⁷BOLLMAN, J L. Peptic ulcer in experimental obstructive jaundice. *Proc Staff Meet of Mayo Clinic*, 1920, v, 357-358.
- ⁸BOLLMAN, J L, and MANN, F C. Experimentally produced lesions of the liver, *Ann. Int Med* (In press).
- ⁹CHAPMAN, C B, SNEEL, A M, and ROWNTREE, L G. Decompensated cirrhosis of the liver. Report of 112 cases. *Proc Staff Meet of Mayo Clinic*, 1930, v, 309-314, *Jr Am Med Assoc*, 1931, xcvi, 237-244.
- ¹⁰ELLIS, ELLSWORTH, and COLE, RALPH. The operation of omentopexy in cirrhosis of the liver, *Surg, Gynec, and Obst* 1919, xxviii, 309-315.
- ¹¹ELLSWORTH, READ. Guanidine base concentration in blood of normal individuals and in patients with liver injury, *Bull Johns Hopkins Hosp*, 1930, xli, 296-306.
- ¹²FEISSINGER, NOEL. Le probleme de la curabilite des ascites dans les cirrhoses alcooliques, *Ann de med*, 1926, xix, 428-440.
- ¹³FEISSINGER, NOEL, and BRODIN, PAUL. Le syndrome ictero-ascitique des hepatites sclereuses, *Presse med*, 1924, 1, 121-123.
- ¹⁴FRANKE, FELIX. Die chirurgische Behandlung des Aszites, *Munch med Wchnsch*, 1930, 11, 2058-2061.
- ¹⁵FRIEDENWALD, JULIUS. The pathologic effects of alcohol on rabbits an experimental study, *Jr Am Med Assoc*, 1905, xlv, 780-784.
- ¹⁶GILBERT, BLUM, PAUL, DUFOURMENTEL, L, and CHRYSSIKOS, J-B. L'examen oesophagoscopique dans les cirrhoses veineuses du foie avec ascite (cirrhose atrophique et hypertrophique), *Compend Soc de biol* 1925, xciii, 1511-1512. *Rev med-chir d mal du foie*, 1926, 1, 9-19.
- ¹⁷GREENE, C H, ALDRICH, MARTHA, and ROWNTREE, L G. Studies in the metabolism of bile III. The enterohepatic circulation of bile acids. *Jr Biol Chem*, 1928, lxxxi, 753-760.
- ¹⁸GREINER, C H, McVICAR, C S, SNELL, A M and ROWNTREE, L G. Diseases of the liver. VI. A comparative study of certain tests for hepatic function in cases of cirrhosis of the liver, *Arch Int Med*, 1927, xl, 159-181.
- ¹⁹HARROP, G A, JR and BARROW, E S G. The excretion of intramuscularly injected bilirubin as a test of liver function, *Jr Clin Invest* 1931, ix, 577-587.
- ²⁰HERRICK, F C. An experimental study into the cause of the increased portal

- pressure in portal cirrhosis Jr Exper Med, 1907, ix, 93-104
- ²¹HOPFNER EDMUND Der Aszites und seine chirurgische Behandlung, Ergebn d Chir u Orth, 1913, 410-480
- ²²HUGHSON, W Portal cirrhosis with ascites and its surgical treatment, review of 26 cases Arch Surg, 1927, xv, 418-440
- ²³JOHNSTON, J M The relation of changes in the portal circulation to splenomegaly of the Bant's type, Ann Int Med, 1931, iv, 772-782
- ²⁴KING, R B The blood picture in portal cirrhosis of the liver A report based on 100 cases New England Jr Med, 1929, cc, 482-484
- ²⁵KIRKIN, B R, and MOFRSCH, H J Report of a case of roentgenologically demonstrable esophageal varices complicating splenomegaly, Jr Am Med Assoc (In press)
- ²⁶KOSTER HARRY, GOLDZIEHER, M A, and COLLINS W S The relation of hepatitis to chronic cholecystitis Surg, Gynec and Obst, 1930, i, 959-963
- ²⁷LIDDE, D M Study of atrophic cirrhosis of the liver in relationship to syphilis, Ann Int Med, 1929, ii, 932-935
- ²⁸LOWY, F L Pseudogallensteinkoliken bei Leberzirrhose und subakuter Leberatrophie Wien klin Wchnschr, 1924, lxxvii 852-854
- ²⁹LOVICO W T Cirrhosis of the liver produced by chronic protein intoxication Tr Ass Am Phys, 1913, xxviii, 407-512
- ³⁰MASS, F C Personal communication
- ³¹MARTIN, G H, BUSTING C H and LOVISHART A S The morphological changes in the tissues of the rabbit as a result of reduced oxidations, Jr Pharm and Exper Therap, 1916, viii, 112-113
- ³²MAYO W J The surgical treatment of hepatic cirrhosis Ann Surg, 1921, lxxix, 410-420
- ³³MAYO W J The surgical treatment of hepatic cirrhosis, Jr Surg, Gynec and Obst, 1921, lxxxi, 112-113
- ³⁴MINOR, A S, and CUTLER, J T Increase in guanidine-like substance in acute liver injury and eclampsia, Proc Soc Exper Biol and Med, 1929, xxvi, 607-611
- ³⁵MORGAGNI, G B The seats and causes of diseases London, A Millar and T Cadell, 1769, p 212
- ³⁶NISSEN, H A Cirrhosis of the liver showing jaundice and ascites An analytic study of 117 cases Med Clin N Amer, 1920, iv, 555-569
- ³⁷OLGARY, P A Observations on the treatment of syphilis of the liver Jr Am Med Assoc, 1931, lxxvi, 183-185
- ³⁸O'LEARY, P A, SNELL, A M, and BANNICK, E G Portal cirrhosis associated with chronic inorganic arsenical poisoning, report of two cases Jr Am Med Assoc, 1928, xc, 1856-1859
- ³⁹OPPI E L On the relation of combined intoxication and bacterial infection to necrosis of the liver, acute yellow atrophy, and cirrhosis Jr Exper Med 1910, xii, 367-387
- ⁴⁰RLISMAN DAVID Spontaneous and operative cure of cirrhosis of the liver, report of illustrative cases Jr Am Med Assoc, 1921, lxxvi 288-290
- ⁴¹RICH, A R The pathogenesis of the forms of jaundice, Bull Johns Hopkins Hosp, 1930, lxvii, 338-377
- ⁴²ROCHESTER HUMPHRY Portal cirrhosis In Christian, H A Oxford medicine New York, Oxford University Press, Pt 1, 1920, iii, 369
- ⁴³ROCHESTER, H D and MCNEIL, J W Discases of the liver gallbladder, and bile ducts London, MacMillan Co, 1929, 881 pp
- ⁴⁴ROWNTREE, L G Considerations in cirrhosis of liver Jr Am Med Assoc, 1927, lxxviii, 1590-1597
- ⁴⁵ROWNTREE L G, KEITH, N M, and BAYLOR, C W Novasurol in treatment of icterus in hepatic disease Jr Am Med Assoc, 1925, lxxxi 1187-1193
- ⁴⁶ROWNTREE L G, WATSON, WATSON, and MURPHY, A H The treatment of icterus in hepatic disease for prevention

- of hemorrhage from esophageal varices, Proc Staff Meet of Mayo Clinic, 1929, iv, 263-264
- ⁴⁷RUOITE Abouchement de la veine saphene externe au peritoine pour resorber les epanchements sciatiques, Lyon med, 1907, cix, 574-577
- ⁴⁸SALL, PAUL Über Salyrganwirkung und Leberfunktion (Beobachtungen an Fallen von Leberzirrhose), Wien Arch f inn Med, 1929, xviii, 397-402
- ⁴⁹VIDAI Traitement chirurgical des ascites Presse med, 1903, ii, 747
- ⁵⁰WHITE, W H The cause and prognosis of ascites due to alcoholic cirrhosis of the liver, to perihepatitis, and to chronic peritonitis, Guy's Hosp Rep, 1892, xlix, 1-42
- ⁵¹WOLF, GUNTHER Die Erkennung von Ösophagus-Varizen im Rontgenbilde, Fortschr a d Geb d Rontgenstrahlen, 1928, xxxvii, 890-893
- ⁵²YANG, C S Cirrhosis of liver, report of 84 cases, Nat Med Jr, China, 1928, xiv, 197-210

Hereditary Ectodermal Dysplasia of the Anhidrotic Type*

By WILLIAM H. GORDON, M.D., F.A.C.P., and ROBERT C.
JAMIESON, M.D., *Detroit, Mich*

IN making a report of this case which we feel belongs to the group described by Goeckermann⁶ in 1920, MacKee and Andrews¹² in 1924, Weech²¹ in 1929 and Jean Smith¹⁸ in 1929, it is deemed hardly necessary to review in detail the cases comprising the list that has been so ably brought up to date by the authors mentioned.

We therefore will give a detailed description of this case and give tables of the chronology and clinical and pathological features to conform

to those in MacKee and Andrews¹² work in order to give uniformity to the reports of cases to date.

This chronological table is compiled from those given by MacKee and Andrews¹² and Jean Smith¹⁸ with the addition of two cases described by Oliver and Gilbert¹⁴ in 1926. After a study of the cases reported by Mackay and Davidson¹³ as "Congenital Ectodermal Defect", they were not considered to have a place in this group which Weech²¹ terms Hereditary Ectodermal Dysplasia of the Anhidrotic Type. Jean Smith¹⁸ believes this a better term for the anomaly

*Received for publication April 1, 1931

TABLE I
REPORTED CASES ARRANGED CHRONOLOGICALLY

1	1848	Thurnam ²²	male	English
2	1848	Thurnam ²²	male	English
3	1848	Williams ⁷	female	English
4	1883	Gulford ⁸	male	American
5	1898	Ascher ¹	male	German
6	1898	Ascher ¹	male	German
7	1902	Tendler ⁹	male	German
8	1911	Wechselmann and Loewy ²	male	German
9	1911	Wechselmann and Loewy ²	male	German
10	1913	Christ ³	male	German
11	1915	Gibbs ⁴	male	English
12	1915	Gibbs ⁴	male	English
13	1915	Strindberg ⁵	male	Swedish
14	1920	Goeckermann ⁶	female	English
15	1924	MacKee and Andrews ¹²	male	Jewish
16	1926	Oliver and Gilbert ¹⁴	male	Polish
17	1926	Oliver and Gilbert ¹⁴	male	Polish
18	1929	Weech ²¹	male	Jewish
19	1929	Weech ²¹	female	Jewish
20	1929	Jean Smith ¹⁸	male	English
21	1929	Jean Smith ¹⁸	male	English

and we agree with her reasons for the use of the title

MacKay and Davidson's¹³ cases showed dystrophy of the hair and nails only, with no change in the sweat or sebaceous glands and none of the other features of the anhidrotic type. These authors present a genealogical chart of affected persons in five generations in which transmission by both sexes is shown.

To this group we feel should be added Clouston's³ analysis of 119 cases in six generations, reported under the title of "Hereditary Ectodermal Dystrophy." These are all dystrophies of the hair and nails and Clouston³ differentiates this type from the anhidrotic type. He found in this group cases of keratoderma palmaris et plantaris and thinks they are residual forms of a disappearing dystrophy. This type involves the epidermis itself, the hair, nails, sebaceous glands and to some extent the sweat glands.

It is possible that there is some relation between the two groups.

The two cases reported by Oliver and Gilbert,¹⁵ while not having all the major defects, are considered by the authors to belong to this group.

CASE REPORT

Patient, G F, female, aged 17, native of Detroit, born of Russian Jewish parents, has been under our care for ten years. Her chief complaint was deficient growth of hair and teeth and inability to sweat. Difficulty in working during hot weather.

Present Illness Patient has noted that her hair was sparse very early and sought medical advice at that time. She was under treatment for a very short time when she discontinued same. In May, 1930, she again sought medical advice in an attempt to remedy her complaints.

Family History Father is living and well. Mother died of heart disease and diabetes at 43. Two sisters and one brother are living and well. No history of a similar disease in the family. One sister age 25, has absence of a few upper teeth with one peg-shaped upper left cuspid. Paternal uncle has manic-depressive psychosis.

Past History The patient has had measles, chickenpox and scarlet fever. Tonsillectomy was done ten years ago. In the past two years her cervical glands became swollen and at that time were painful. In winter these glands swell up once a month and remain so for a few days. She has frequent nose bleeds. There is a history of convulsions until ten months of age. She was delivered by instruments. History by systems is negative.

Physical Examination Height five feet, five inches. Weight, 124½ pounds. Blood pressure, 120/70. There is a peculiar lack of hair on scalp and face (eye-brows), axillae and pubis. Hair which is present over scalp and pubis has appearance of lanugo hair and is very scant, fine, dry and almost crisp and close to skin. Skin around upper and lower eyelids is pigmented. Lips are thickened. Skin is dry, cool and scaly in places. Face presents freckles. Forearms show faint brownish pigmentation over extensor surface. Eyebrows are lacking excepting a few hairs at midline. There is no hair in the axillae or on forearms and legs and but few hairs on mons Veneris. The eyes are small and set close together. The pupils are large, round and equal react to light and accommodation. The nose is of a marked saddle-shape and the nares small. Foul odor of ozena comes from the nose and upon examination with speculum the septum is found to be partially destroyed. Grey necrotic material is present. The mouth is narrow, the lips prominent and thick and the mouth is poorly kept. The teeth are in poor condition. Though but one has been extracted one notes the absence of a large number. Those that are present are of a peculiar shape (peg-shape) and misplaced so that it is impossible to tell which are missing. The buccal membranes appear to be healthy. There remains a left tonsil tag. The neck glands are negative.

TABLE II
CLINICAL FEATURES OF REPORTED CASES

Individuals	Oliver and Gilbert 1926 John Z.		Oliver and Gilbert 1926 Joe Z.		Weech 1929	J. Smith 1929	Falconer 1929	Gordon and Jamieson 1931 G F	
	10	16	14	7	5	6	17	female Jewish	3
Case 1	male Polish	male Polish	male Jewish	female	male English	male English	female Jewish		
Number brothers and sisters	3	3	2	2	3	2	3		
Number brothers with defect detected	1	1	1	0	0	0	0		
Number and defects in other teeth	0	0	0	2 paternal great uncles with defective teeth	0	0	0		
Number of antecedents	none	none	single	none	single	tabes in father	0		
Number of single cases in children	0	0	0	single	0	single	single		
Number of cases definitely inherited	none	none	none	0	0	none	0		
Number from father	none	normal	normal	none	normal	normal	none		
Number from mother	yes	yes	yes	yes	yes	yes	yes		
Number from both	sparse	sparse	sparse	sparse	sparse	sparse	sparse		
Number and cases with	fine dry	fine dry	fine dry	fine dry	fine dry	colorless down	fine dry		
Number of cases with	none	none	none	none	none	none	none		
Number of cases with	present	present	sparse	scant	scant	scant	scant		
Number of cases with	none	beginning	scant	scant	scant	scant	scant		
Number of cases with	none	none	scanty	none	none	none	scanty		
Number of cases with	no	no	yes	yes	yes	yes	yes		
Number of cases with	no	no	yes	no	yes	no	yes		

[illegible]



FIG. 1. Photograph of patient in 1926.

TABLE III
MICROSCOPICAL FINDINGS IN SKIN IN REPORTED CASES

	Oliver and Gilbert ¹⁴	Weech ²⁴	Weech ²⁴	J Smith ¹⁸	Falconer ⁴	Gordon and Jamieson
Location	none reported	none reported	none reported	anterior chest and axillary line level with nipples	thumb	inguinal region
Sweat glands	none reported	none reported	none reported	none	none	none
Hair follicles and arrectores	none reported	none reported	none reported	none	none	none
Sebaceous glands	none reported	none reported	none reported	none	none	none
Epidermis	none reported	none reported	none reported	no des- cription	well dif- ferentiated and high de- gree of ker- atinization	layers normal
Derma	none reported	none reported	none reported	none	normal mus- cle fibres well devel- oped	normal
Elastica	none reported	none reported	none reported	none		normal

The thyroid shows a small adenoma. The areolae of the breasts are 7 mm in diameter. The breasts are flat and poorly developed so that very little breast tissue can be palpated. Otherwise the chest is negative. The abdomen is normal.

The patient presents a facies of a Mongolian type and looks anything but intelligent but upon questioning her one finds that she is above the average at school. She is seventeen years of age and in the 11th A grade. She plays the piano well. Her voice is husky, dry and squeaky. All *Reflexes* are normal. The arms well formed and shaped, fingers pointed, legs well formed and shaped. On the right knee there is a scar from injury.

Provisional Diagnosis at onset: Congenital lues and Hutchinsonian teeth.

Laboratory Data: Urine negative. *Blood Wassermann negative*, *Spinal fluid Wassermann negative*. Spinal fluid showed a negative cell count. Blood count on May 15, 1930: hemoglobin, 83%, red blood cells,

3,910,000, white blood cells, 16,800 polymorphonuclears, 79% lymphocytes, 14%, eosinophils, 4%, mononuclears 3%. On Oct 6, 1930 the blood count was: hemoglobin, 80%, red blood cells 5,370,000, white blood cells, 9,500, polymorphonuclears, 50%, lymphocytes, 41% mononuclears, 7%, basophils, 1%. The electrocardiogram was normal. Blood chemistry findings on Oct 5, 1928 were as follows: blood sugar, 0.100, N.C.N., 28.6, cholesterol, 136. On Oct 13, 1928 blood sugar, 0.095, Ca 8.4, Phos 2.78. On Oct 17, 1928 uric acid 4.28. B.M.R. Oct 9 1928 minus 11%. Repeated B.M.R. Oct 11 1928 minus 11%. Oct 20 1928, minus 20%. Goetsch skin reaction, Oct 14 1928 normal.

Histologic Description of Skin (Lido J. Wile, M.D., Professor of Dermatology, University of Michigan). The epithelium is about normal in thickness. Here and there on the surface is a patch of hyperkeratosis. The various layers of the epidermis are normal. The stratum granulosum is ill de-



FIG. 2. Pre-operative patient taken in 1950



FIG 3 Side view of patient in 1930

fixed. The hemalum and eosin specimen shows a fairly dense subcutaneous tissue with considerable fragmentation of the collagen bundles. The striking feature of the subcutaneous tissue is the complete absence of both hair follicles, sebaceous glands, and sweat coils and ducts. The Van Gieson stain shows the collagen bundles well defined, but distinctly fragmented. The subepithelial elastica is well stained, and shows no abnormality. The resorcin-fuchsin, lithium carmine preparation shows the elastica well distributed throughout the section and apparently no diminution or fragmentation of the collagenous bundles, and a complete absence of the entire pilo-sebaceous system and of the sweat coils and ducts.

Description of the Teeth (H. F. Doane, DDS, of Detroit, Michigan). X-ray examination was made on March 24, 1931. This examination consists of eleven intra-oral films. At the present time the upper arch contains seven teeth and the lower arch five teeth. The patient gives a history of having had the lower left molar extracted. So far as can be determined, thir-

teen teeth are all the patient ever developed. None of the teeth which have erupted present the usual anatomic features. The upper right and left molars appear as bicuspid with an extra cusp, that is, the occlusal surface does not present the usual grooves and cusps of a molar. The appearance is very similar to the occlusal surfaces of the bicuspid, with the exception of the fact that there are two buccal cusps instead of one. The tooth occupying the lower right molar region presents anatomical features almost identical with the bicuspid. The roots of all molars appear single, although there is more than one root canal, indicating fused roots instead of the normal bifurcations. The teeth occupying the normal position of the upper central incisors present anatomical features very similar to the upper cuspids. The remaining seven teeth appear as the so-called peg teeth, their crowns being cone-shaped and presenting little or no anatomical marking. The tooth occupying the upper left lateral incisor region appears to be deciduous. At this time, its root is resorbed.



FIG. 1. X-ray films of the teeth of the patient.

and the tooth is very loose. The enamel of the teeth which have formed and erupted is of usual thickness, but to date no microscopic study of tooth tissue from this patient has been made. Clinically and roentgenographically the structure of the enamel, dentine, pulp chambers and pulp canals appears as usual. Neither the extraoral nor the intraoral films of the patient's jaws reveal any evidence of unerupted teeth, and no tooth buds or malformed tooth tissue is evident. In the upper right bicuspid region we note an area of decreased density which appears to be poorly calcified bone. A similar area, but less extensive, is shown in the upper left bicuspid region. Roentgenologically, the bone in the lower right and left bicuspid regions, where no teeth ever developed, appears somewhat compressed, as compared with the regions in which teeth have developed. Otherwise the body structure of both jaws is quite usual in appearance on X-ray examination.

DISCUSSION OF GENERAL CHANGES FOUND ON SKIN AND APPENDAGES

The hair of the scalp was fine and grew sparsely over the entire scalp. It seemed to be of a normal length but was of soft texture and grew slowly. The eyebrows were lacking except at the inner third where a few hairs were found. The eyelashes were few and scattered along the border of the eyelids.

A few short fine axillary hairs could be detected on close examination as well as a very slight lanugo growth on the body, arms, upper lip and cheeks. This growth was practically invisible without the use of a magnifying glass. Pubic hairs were scanty.

Supraorbital ridges were prominent. No pseudorhagades were found but the vermillion borders of the lips were definite though not marked. The sense of smell and sense of taste were stated to be normal.

The bridge of the nose was depressed in the typical saddle-back formation, a chronic rhinitis was present with an accompanying foul odor. The general impression of the face was that it was of the Mongolian type.

The palms and soles presented many fine criss-crossed lines, were smooth, dry and shiny, giving the feeling of a dry skin tightly stretched over underlying structures. The finger nails and toe nails presented no abnormalities.

In the center of the back over the spine of the interscapular region and also over the scapular areas were three groups of minute papular lesions of non-inflammatory type suggestive of keratosis pilaris.

The entire skin was very white, fine, smooth, soft, glossy, pliable and dry.

SUMMARY

A case is described presenting the major defects of anhidrosis, alopecia, dental aplasia, nasal rhinitis and saddleback nose with absence of sudoriparous apparatus.

Tables are presented with cases reported in the literature in chronological order up to the present time. A tabulation of symptoms of those reported since 1924 and a tabulation of microscopic pathologic findings are also given.



FIG. 1. *Phaeocephalus* sp. (100 \times)



FIG. 6 Higher power magnification of skin. The entire pilosebaceous system is present.

REFERENCES

- ¹ASCHIR, B Geschwister mit Anomalien der Ohren, der Zahne und der Haut, Verhandl d Berl Gesellsch f Anthropol, 1898 114-121
- ²CHRIST J Ueber die kongenital ekto-dermalen Defekte und ihre Beziehungen zu einander, vikariierende Pigment für Haarbildung Arch f Dermat u Syph, 1913, cxvi, 685-703
- CROSTON, H R Hereditary ectodermal dystrophy, Canad Med Assoc Jr, 1921 xvi, 18-31
- ⁴FALCONER, A W Congenital ectodermal defect, Lancet, 1929, ii, 656-658
- GIPPS, J H Total absence of teeth in two brothers, Dental Record, 1915, xxxi, 669-671
- ⁶GOICKERMAN, W H Congenital ectodermal defect, report of case, Arch Dermat and Syphil, 1920, i 396
- ⁷GUTHRIE, S H A dental anomaly, Dental Cosmos, 1883 xxi, 113-118
- ⁸GILFORD H Progeria, a form of senilism, Practitioner 1904, lxxiii, 188-217
- ⁹HARRIS, H Disease of ectodermal origin, Jr Am Med Assoc, 1923 lxxx 812
- ¹⁰HUTCHINSON, J Congenital absence of hair and mammary glands with atrophic condition of skin and its appendages, Medico-Chirurgical Trans, 1886 lxxx, 473-477
- ¹¹KJEMP, J A case of congenital total absence of permanent teeth, Dental Cosmos, 1907, xlix, 924-928
- ¹²MACKEE G M, and ANDREWS, G C Congenital ectodermal defect, Arch Dermat and Syphil, 1924 x, 673-701
- ¹³MACFARLANE H and DAVISON A M Congenital ectodermal defect Brit Jr Dermat 1920 xli 1-5
- ¹⁴MACFARLANE H and GILBERT N C Congenital alopecia Arch Dermat and Syphil, 1929, xiii, 359-373
- ¹⁵MACFARLANE H, and GILBERT, N C Congenital alopecia with ectodermal defects, Jr Am Med Assoc, 1931 lxxxviii 1331
- ¹⁶PAPASTRATIGAKIS, C Dystrophic syndrome, Paris Med, 1922, vii 475-476
- ¹⁷RUSHTON, W The total absence of dentition in a boy aged sixteen, Trans-Odontological Soc Gr Br, 1904, xxxvi 199-204
- ¹⁸SMITH J Hereditary ectodermal dysplasia, Arch Dis Child, 1929, iv, 215-226
- ¹⁹STRANDBERG, J A contribution to question on the malformations of the ectoderm due to arrested development Nord Med Ark, 1918, li Part II 1-12
- ²⁰TENDLER, B Ueber angeborene und erworbene Atrophia cutis idiopathica Arch f path Anat, 1902, clxvii, 465-490
- ²¹THADANI, K I A toothless type of man Jr of Heredity, 1921, vii, 87-88
- ²²TURNHAM J Two cases in which the skin, hair and teeth were very imperfectly developed, Medico-Chirurgical Trans, 1848, xxxi, 71-82
- ²³LOEWY, A, and WICHSCHMANN, W Zur Physiologie und Pathologie des Wasserwechsels in der Warmeregulation seitens des Hautorgans, Arch f path Anat, 1911, ccvi, 79-121
- ²⁴WITCH, A A Hereditary ectodermal dysplasia (congenital ectodermal defect), report of two cases Am Jr Dis Child, 1929, xxxvii, 766-790
- ²⁵WHITTON, H Clinical significance of congenital absence of upper lateral incisor teeth, Endocrinology 1925 ix, 35-60
- ²⁶WHITING, PIERRE Aus dem Gullhane Lehr-Frankenhaus in Konstantinopel Angeborener vollkommener Zahnangel, Deutsche med Wochenschr, 1911, xxxvii 504
- ²⁷WHITTING, C J B (Young child with congenitally absent upper lateral incisor teeth), London Med Rec, 1912, xli, 376

The Application of a Modified Psychiatric Approach in the Treatment of Certain Gastro-Intestinal Disorders*†

By THODORE H. MORRISON, M.D. F.A.C.P. and SAMUEL MORRISON, M.D. *Baltimore, Md*

IT has long been recognized that a large number of patients who come under the care of the gastro-enterologist are psychoneurotic and one wonders whether the gastro-enterologist is able to treat these patients satisfactorily or whether they can be better cared for by a psychiatrist. A consideration of the type of psychoneurosis, its duration, its status praesens, etc., makes this decision less difficult. In those instances in which the psychoneurosis is very mild and is referred to the gastro-intestinal tract particularly where the patient is fifty years or older, it is our opinion that a more satisfactory outcome can be obtained if the patient is under the control of a capable gastro-enterologist.

A gastro-enterologist should be thoroughly familiar with psychiatric measures if he hopes to succeed in caring for these patients. On the other hand, we are convinced that a capable psychiatrist cannot be expected to be a gastro-enterologist. In either event it is conceded that the individual patient

must be considered primarily but the best and most permanent results according to our experience are obtained by the physician whom we may call the gastro-psychiatrist. The latter sees no reason for unearthing complexes delving into the subconscious and thereby magnifying the patient's troubles. He has no objection to the simultaneous use of both medical and psychotherapeutic forms of treatment. He is not aware of any danger in administering a medicinal treatment to a psychoneurotic nor does he decry its supposed detrimental effect. He does not stress too strongly the "nervous" element in the patient's personality because he knows from experience that little or no benefit is derived from such a procedure. He does not hesitate to treat the disease and to give the patient symptomatic relief while he studies the individual as a whole for he realizes through a long-continued association with these individuals that this plan inspires more profound confidence and that it leads to a so-called cure which is more lasting and less time-consuming. Above all he avoids deception and yet he employs a practical psychotherapy which neither

*From the Gastro-Enterological Clinic of the Department of Medicine, University of Maryland

†Received for publication April 20 1931

stamps the patient as psychopathic, nor allows him to consider himself entirely normal

How does the gastro-psychiatrist study his cases? He, of course, realizes that treatment, as well as disease, cannot be standardized. He therefore makes the usual complete study including a good history, a brief personality study, a physical examination, the indicated laboratory procedures and any special studies which seem advisable. All these he considers essential parts of psychotherapeutics. If after such a thorough study no organic basis for the patient's symptomatology is noted he can offer reassurance in a manner which is most convincing. In this way he not only gains the patient's confidence but makes the first step in the needed reeducation. In his conversations much is learned concerning the patient's reactions and this aids in pointing out the correct plan of treatment. The symptoms are genuine and if drugs will relieve these, they are temporarily employed without fear of dire consequences. Rest, diet, exercise, occupational therapy are utilized as indicated. Where hospitalization seems advisable a general hospital or sanatorium is selected depending upon the status of the patient. Sometimes a change in environment alone is a most valuable therapeutic measure. It is surprising how willing a patient is to cooperate with a gastro-psychiatrist and how frequently the former gradually learns that "nervousness" is the only cause of his disturbance. In only a few cases is it necessary to resort to drugs, and these are used for the purpose of relieving the patient's physical discomforts. The patient is then encouraged to follow a

relationship between physician and patient the factors concerned in the latter's maladjustment are unraveled with much less difficulty. We have seen the most sensitive patients gradually become desensitized by such an approach and more extraordinary is the fact that the sequence of events leading up to the present illness explain themselves automatically. There is, however, a certain group of individuals who do not respond so well. These are usually cases who have consulted many physicians, going from one to another without allowing time for sympathetic understanding and adequate treatment. However, in some instances even such individuals have been helped by the procedure which we advocate. Often the mental effect of a complete examination with an explanation of the condition and reassurance results in a "cure." For example, this occurred in many patients who presented themselves with a cancer phobia and in whom this idea was not only recognized early but dispelled as a result of a complete study.

In many of our cases we have observed that with individuals who lack average intelligence the response to psychotherapeutic measures is unsatisfactory, whereas the treatment of a symptom or an organic condition (if that exists) is impressive and in itself becomes an efficient psychic measure. For instance, the mere application of a support in a patient with enteropneosis or pendulous abdomen even though these conditions may have little to do with the production of symptoms may relieve physical discomfort that would otherwise follow. Many

other examples could be noted but the idea which we wish to emphasize is that this group does not lend itself to pure psychic appeal for there is little to appeal to. On the other hand, these individuals respond to medicine and physiotherapy because these measures inherently carry with them suggestive properties.

Witness this instance, related by Bland Sutton,¹ of a psychiatrist who made excellent use of a frog in the following circumstance. "A thin and foolish woman believed she had accidentally swallowed a frog and that her thinness was due to the frog eating the food in her stomach. In order to dispel the illusion the doctor gave the patient an emetic and during the vomiting he slipped a frog into the basin. When the patient saw the frog her joy was great, but in a few minutes her depression returned. 'Oh!' she exclaimed, 'I am sure this frog has left some young ones in my stomach.' The doctor looked wise, pulled out his magnifying glass, and after critically examining the frog said unto the patient, 'Fear not, this frog has not left any froglets inside you, behold, it is a male!' The patient was quite satisfied, became happy and in a few months was plump again. She was not a naturalist, and therefore ignorant of the fact that it is difficult to tell the sex of frogs by mere inspection except at the breeding season."

We should like to direct attention to another group of cases in which any form of psycho-analysis is contraindicated. When a patient is examined one often realizes that no progress will be made unless personal matters are investigated. However,

there have been many individuals who consulted us after they had bitterly resented what they deemed irrelevant and unnecessary questioning directed towards their private affairs at the hands of psychiatrists. We have seldom found it necessary to inquire into sexual relationships, marital incompatibilities, financial affairs, social and religious difficulties. In some cases the patient is aware of an underlying maladjustment and is able to combat it if his mental attitude is changed through a process of reassurance, encouragement and relief of symptoms. In other instances, the individual fails to recognize any underlying psychical causes and not only seeks but insists that a physical basis be discovered. In this group a tactful, delicate and sympathetic approach opens up more avenues of willing discussion than could be obtained by the immediate attack upon repressions, inhibitions, the subconscious, and so forth. It is certain that every one of us has built up a defense mechanism which is the basis upon which our adjustments to our environments rest. To shatter these structures is dangerous. They are the buildings resulting from years of construction, tampering with them is unwarranted. Psychiatrists often seem unaware of this fact.

It is generally admitted, as Reynolds² states that a fundamental principle of the treatment of neurosis is based upon an explanation to the patient of the evolution of his nervous symptoms from their original sources. In our experience there are a large group of cases in which such explanations are best omitted. It is proper to ascertain the causative factors in-

volved in each individual case but it is not well to break down a moderately substantial foundation because one feels that the patient should conform with the majority. If we learn that the neurosis is dependent upon certain sexual problems, certain environmental conditions, certain physical handicaps, etc., these can be adjusted in many instances without the patient's knowledge and with much better effect. Many of these individuals gradually become self-explainers and their pride in having discovered and treated themselves is in itself a great conquest. Like the obstetrician we must preach "*noli me tangere*" in this group of cases which will become more and more well defined as time proceeds. We realize all the old arguments about the necessity for strengthening individuals with neuropathic streaks, inferiority complexes and unstable nervous equilibria but we know from an ever growing experience, that the best procedure is not to have the patient become conscious of his shortcomings.

Preventive medicine³ plays its psychiatric rôle which is concerned among numerous other things, with the routine and regular overhauling of the type of the patient with whom we are concerned. It is on this account that we advise our patients to visit us at regular intervals. After all, who can determine exactly where the normal limits stop and the abnormal begin, where, for example, the micro-manic-depressive (Overstreet⁴) becomes the manic-depressive. If we are indulging in such vagaries let us give the patient the benefit of the doubt and let us not convince him and ourselves that he

is mentally sick without due evidence. Just as the psychiatrist errs on his side, so the internist, as Reynolds remarks, "is liable to fail if he does not study carefully all the features of the case before starting to treat it." "The difficulty" he continues, "is that the medical practitioner is in danger of becoming so absorbed in the treatment of any obvious organic pathology that he may fail to pay attention to the neurotic symptoms which are its result. On the other hand, if the neurotic element is predominant, it is equally easy to overlook the apparently trivial physical abnormalities which may have been contributory factors in the disturbance of the nervous equilibrium. In order to steer a middle course between these two common errors, it is well to assume that every case has both an organic and a functional element."

It is generally known that most psychopathic persons with gastrointestinal complaints (as well as society in general) fear the stigma of having any professional contact with a psychiatrist. Certainly this reaction should not exist but since it does, it is best to recognize it. We agree with Alvarez⁵ that one must be fitted temperamentally for the problem presented by these patients. Since the gastro-psychiatrist is familiar with certain syndromes in his specialty it is more probable that he can evaluate the symptom-complexes and plan a rational form of treatment suited to the individual. He certainly realizes that there is a large group of cases in which the mechanism of the affection must be explained in order to obtain satisfactory results. Such an example

may be present in the following instance taken from Oliver⁶ "When a woman who has had phobia of cancer all her life and who has restricted her diet so that she is skin and bone because she has an idea that rough food irritates the stomach and produces cancer there,—when she can be brought to realize that her mind has been sensitized to the fear of cancer because of her distressing experiences with a beloved father who died of it—why, you have already robbed her phobia of a good part of its nameless overshadowing horror" He is also aware of those cases in which patients substitute one obsession, one disease, one anxiety for another. Jelliffe⁷ has called attention to instances in which cures of various "diseases" were obtained sometimes with the aid of surgery only to have another and often less vulnerable affection arise. It must be understood that this method of treatment is offered only in a certain selected group of cases. There are patients with whom one must insist on the mental basis of the affection. Care must always be taken, however, not to plunge the patient into hypochondriasis (Dubois⁸) and one must always have "sized-up the situation" before proceeding in this manner.

To make our position clear, we do not claim a cure-all, we simply offer a method, not different in kind but in principle. In brief, we do not believe that the majority of these gastro-psychoneurotics are best treated by psychiatrists since from the very beginning the former are antagonistic to psychiatrists and where antagonism exists good therapeutic results are wanting. In the treatment we aim as

far as possible, at prompt symptomatic relief. The relief of symptoms leads to a more pliant mental and physical attitude. The fear with which certain psychiatrists administer drugs is commendable in some cases but not, as a general rule, in gastric neuroses. Gastric symptoms can be relieved without the danger of formation of drug habits or other untoward effects.

In order to illustrate more clearly this modified medical and psychiatric approach 200 consecutive gastro-intestinal cases in our clinic were studied. Of these, fifty showed etiologic factors which were definitely psychogenic while in the rest the nervous element was more or less prominent. In every instance, however, the chief complaint was referred to the gastro-intestinal tract. Each patient was subjected to the complete study already mentioned, nothing was assumed. Upon the basis of this examination treatment was instituted.

A few abstracts of illustrative cases follow.

Case I J. L. S., male, (a salesman) aged 60, complained of "stomach trouble and nervousness" of two years duration. The patient was aware of the fact that his mother had died of hypertensive heart disease. In the past he had had the usual childhood diseases with no complications but about ten years ago, following a so-called "mild stroke", he became very weak requiring about three months before he fully regained his faculties. A review of the systems discloses the following important data—nocturia, three or four times very nervous, some insomnia, occasional spell of dizziness and weakness, tires quickly, has many obsessions. Little except the enumeration of some vague digestive symptoms could be learned of the present illness. In other words there was a gastro-intestinal fixation.

On physical examination, the general appearance was one of depression in a well nourished and well-developed elderly man. Briefly, the positive findings were dilated pupils reacting normally, ophthalmoscopic examination normal, lungs normal. The heart was normal in size, the sounds were regular, loud and forceful. Blood pressure 200/120, with no constant associated symptoms. The radials were tortuous and moderately thickened. Abdomen normal. Reflexes normal. The mental examination disclosed many traits of the parergastic reaction type but anxiety neurosis seemed more likely. The urine showed one plus albumin, three plus glucose, a few hyaline casts and white blood cells. Other laboratory examinations were normal.

Our impressions were arteriosclerosis, hypertension, anxiety neurosis, questionable chronic nephritis and questionable diabetes mellitus. Hospitalization was advised. Further studies showed the "diabetes" to be of the nature of renal glycosuria, while no evidence of kidney damage was adduced.

The patient was seen daily, treated symptomatically, spoken to rationally and semi-analytically. Under the administration of mild hypnotics he rested quietly. Gradually his obsessions became less marked. At the same time he began to realize that his principal difficulties were due to "nervous" factors. As far as allowable we stressed his physical fitness, creating simultaneously a restful, reassuring environment and relief of symptoms. The patient, on the other hand, proceeded a step further and diagnosed his case "nervousness." Today, six months later, this man is back in business, working efficiently. He recalls that he was "slightly mentally ill" and is very thankful that we had prevented his relatives from sending him to a mental hospital. It is very unlikely that this patient will have another "nervous breakdown" but should this happen he will certainly seek immediate aid. At the age of 60 he is made fit to work in a certain environment by a mild sort of treatment lasting four weeks.

Case II G. N. C., female, student, aged seventeen years, complained of "gas on stomach" and dizziness. The family and past histories are essentially non-contribu-

tory. The present illness dates back four years when belching was first noticed. For two years there were exacerbations and remissions but gradually the belching became almost continuous and this with a sense of dizziness and emotional instability have persisted to the present time. The physical examination was normal in every detail. The urine and blood were normal. The stool showed two plus mucus. She was unable to swallow the tube for a gastric analysis. X-ray studies disclosed no organic defects, the pylorus was spastic and the colon markedly prolapsed and spastic. In a casual but quite thorough mental examination no alarming findings were noted.

Our impressions were aerophagia, nervous indigestion, and a spastic gastro-intestinal tract. The patient was placed on a schedule of exercises with rest periods and a prescribed dietary regime. In addition she was given certain medicinal preparations combining sedative and antispasmodic properties. Aerophagy was explained to her. Psychotherapy was made to appear incidental.

Under monthly observations a steady gain in weight has been noticed, she has become more stable emotionally and as she remarks, "feels almost well." No attempt was made to blame the entire condition on nervousness although the mechanism of aerophagia was explained in detail. The medications are gradually being reduced but without their psychic as well as medicinal effects, we feel certain that our success in this case would have been much less marked. The "cures" are not temporary since the patient returns at appointed intervals for a check-up and is not discharged until she has a well-established understanding of her difficulties. She is convinced that no organic disease exists and as each visit culminates she realizes more and more that hers is a functional abnormality and gradually she concludes that it depends upon her emotions. The patient credits herself with this discovery and in this attitude lies strength. If the usual psychiatric approach were attempted in a reaction pattern of this kind the problem would have been much more difficult even if the patient's cooperation were taken for granted.

Case III R B, male, shoe-merchant, aged 31 years, complained of constipation and "stomach trouble" characterized by "panicky feelings" and nausea. The family history was non-contributory. In the past there have been four operations over a period of nineteen years. The patient has always been of a highstrung, excitable and unstable nature smoking excessively and imbibing alcoholic beverages occasionally. The present illness is said to have begun three years ago when it was noticed that an already marked constipation was becoming more severe. Symptoms of dizziness, palpitation, "spots before eyes" and general unsteadiness were experienced, and the patient believed he was slowly being poisoned through intestinal stasis. Depression was well on its way but due to certain business matters his mind was occupied for some months. He managed to get along, building symptom upon symptom until six weeks ago when, following the extraction of a tooth, there was a little more than the usual amount of bleeding. He became extremely nervous and apprehensive, a multiplicity of symptoms appeared, his constipation became more uncontrollable than it had ever been, pains and aches were experienced throughout the abdomen, and nausea and loss of weight were noticed. He was on the verge of a mental collapse when seen.

On physical examination he was found to be of asthenic habitus, well developed but only moderately well nourished. He appeared worried and depressed. The head, heart and lungs were found to be normal. Blood pressure, 120/80. Pulse, 90. The abdomen was soft, semi-relaxed and with the exception of a hernial repair scar in the left inguinal region presented no abnormalities. The genitalia, extremities, skin, etc., were normal. Reflexes were very active. The urine and blood examinations were normal. The stool contained a considerable amount of mucus. The Ewald test breakfast showed a total acidity of 82, free hydrochloric acid, 65. The Wassermann reaction (blood) was negative, phenol-sulphonephthalein test showed 55 per cent excretion in two hours (intramuscular injection), blood chemistry studies normal. X-ray studies revealed a prolapsed colon

and stomach with a probable chronic appendix.

In addition to his mental upset, therefore, he had intestinal stasis, enteroptosis and a probable mucous colitis.

The patient seemed greatly relieved when told he had no organic lesion but he was advised to enter a hospital for treatment. The effect of a complete examination with a careful explanation of the condition and reassurance had not only gained his confidence but had already started him on the road to recovery. Correction of the constipation was achieved by means of diet, enemata, etc., leading finally to bowel re-education. In addition rest, exercise and a well rounded daily routine including a requisite amount of diversion were employed and throughout, a sensible and unobtrusive psychotherapy was practiced. A rapid restoration to normal occurred.

This patient has been in communication with us by mail for a half year. He has gained weight steadily and seems to be getting along splendidly. From the tone of his letters we feel that we need not fear a "nervous breakdown" in the near future.

We must remember, as Alvarez² cautions, that "many of the people who complain bitterly of auto-intoxication symptoms are usually sensitive and keenly aware of what is going on in their bodies. It is this sensitiveness which distinguishes them from those who can go for a week quite unconscious of the fact that their bowels are crammed with feces." In addition all of us recognize the fact that "sensory impulses from the digestive tract can profoundly influence our emotions, our mental processes and our vasomotor balance." We recall the young woman who, although symptomless, was extremely frightened because she ordinarily had a bowel movement every five days and at the time of her visit to our clinic had not had a stool for eleven days. Her fears were allayed

after a thorough study and a corresponding effect was soon noticed on bowel function

There is a group of patients who are so ill-informed about their illnesses that one feels it necessary to instruct them to some extent concerning the mechanics of the digestive tract. This is certainly a hazardous business but in our experience one of two procedures may be followed — either give a thorough explanation of the condition or have it understood that the patient's ideas of the disease are erroneous and that its treatment is to be entrusted entirely to the physician in charge.

In the case of R. G. (*Case IV*), female, aged 44, the complaint was referred to the stomach. She was found to have mucous colitis. It was explained that the examinations disclosed no organic disease but she could not be convinced that her symptoms could be due to a non-organic condition. She objected to our assumption that she was a very nervous woman. It was decided to study the case in the usual psychiatric fashion but recovery was slow, tedious and never quite satisfactory. This is to be compared with H. R. S. (*Case V*), female, aged 33, in whom the same situation was met. In this case no explanations were given but various forms of medicinal therapy in addition to diet and rest were employed. At each visit, we suggested that she was certainly much better as revealed by our examinations. Drugs, never given at random, were changed to relieve gas, spasm, intestinal stasis, etc. With this form of therapy, she was brought back to usefulness in a short time. These are examples of a large group of cases which we have observed and in our experience, the latter form of treatment is much more satisfactory not only as to its immediate effect but also as to the permanency of cure.

In *Case VI*, D. V. D., a very nervous ung woman of 34 years with many

vague digestive symptoms, the instructions given were briefly as follows: "Conditions of this type necessarily involve the nervous system and it is important in considering your case to recognize this factor. Any treatment, therefore, which is undertaken, should be directed not only to the digestive tract but equally as well to the nervous system. I should therefore advise you to continue with the dietetic regime (spastic colitis), which I have given you, get considerable rest, wear your abdominal support (enteroptosis with symptoms) and get a reasonable amount of exercise. Your surroundings should be bright and cheerful and you should try as far as possible to overcome all irritations. For the constipation mineral oil is useful. A nerve tonic is advisable and the administration of hydrochloric acid (achlorhydria) with pepsin is also very helpful. I know that you will do well and I shall be very glad to cooperate with you in any way I can to help you regain your health." This, with its implied suggestions, later to be gradually amplified, serves as a basis by means of which the patient acquires the method of studying her personality.

Case VII B. M., female, aged 41 had always complained of gastro-intestinal difficulties. She had run the gauntlet of medical and surgical treatments. A complete study led to the belief that we were dealing with an unhappily married, pronounced hypochondriac whose greatest desire was to remain a chronic invalid. In cases of this type a complete psychiatric study is indicated and we therefore referred this patient to a competent psychiatrist who finally informed us that the patient would not cooperate with him and had decided to get another doctor. This type of individual often does not respond to any type of treatment and sometimes becomes institutional material. Another problem presented itself in the case of S. H. W., *Case VIII*, who had, in addition to a penetrating ulcer at the pylorus, a depressive psychosis which demanded institutional care. Here psychiatric and gastro-enterologic cooperation was necessary.

Case IX L. S., female, aged 20, complained of heartburn and a feeling of full-

ness in the epigastrium. A complete work-up led to the following impressions — Aerophagia, enteroptosis, spastic colitis, intestinal stasis, and "neurasthenia." The patient was so emotionally upset that she was hospitalized since we felt that she could not, despite every effort, modify her mental state in her present environment. Subsequent studies revealed the fact that the patient's instability was due to a shock occasioned by the death of a very dear friend. To this she reacted with what she recognized as a gastro-intestinal upset. Her treatment consisted of reassurance, diet, rest and medicinal therapy (to relieve "heartburn" and "gas formation"). She gradually recovered and it was only after she was rid of her belching and constipation that the probable association with her friend's death was discussed. She reacted admirably.

Case X W R, male, aged 33, complained of "stomach trouble" with vague abdominal discomfort which he believed was due to his "nerves." After a thorough study he was told that he was organically sound and that he had what was called "nervous indigestion." It was explained that strict adherence to a prescribed regime and his complete cooperation would doubtless rid him of his difficulty. He responded well and when last seen it was clear that he recognized the mechanism of his gastrointestinal upset.

Case XI G S, male, aged 27, presented a similar picture complicated by a subacute appendix. He feared an operation but after a week's observation, during which time the signs in his right lower quadrant remained quite definite, he submitted at our advice. Pre-operative and post-operative care were made to include sufficient analgesic preparations so that he would be spared the least pain. (He seemed to be mentally hyperesthetic.) Today, three months after operation, he is getting along splendidly and remarks that his fear of pain has disappeared.

Case XII E I F, male, aged 44, entered our clinic with many gastro-intestinal complaints which appeared when his home physician, during a periodic health examination, mentioned the necessity for ruling out cancer in certain cases. This suggestion was sufficient to set up a cancer

phobia in this individual and unconsciously he reacted with the production of numerous gastro-intestinal symptoms. The examination by us disclosed a spastic colon which responded to antispasmodic therapy. Recovery, finally, was complete, when unsolicited he was told emphatically that he 'absolutely had no cancer.'

Although emphatic reassurance is the coup d'état, straggling symptoms must be treated since their persistence may cause some patients to doubt the physician's diagnosis even though they have utmost confidence in him. An instance of the latter is the *Case XIII*, M S, female, aged 52 who was told by her physician that although her symptoms suggested gall bladder disease examination seemed to indicate a normal organ. Her symptoms persisted, however, and she visited an esteemed clinic where she was informed that only immediate cholecystectomy would afford her relief. This frightened her greatly. Several months later the patient visited our clinic where she was found to be extremely apprehensive and to have a definite mild cholecystitis. She was reassured and when her organic disease responded readily to the method of non-surgical biliary drainages of Lyon her apprehensiveness vanished.

Finally, *Case VII*, is outlined briefly because it teaches so valuable a lesson. W K, female, aged 42, is an example of that group of patients who talk incessantly of their symptoms and who unfortunately are immediately stamped as neurotics. As a matter of fact, careful examination often discloses an organic illness. W K had passed from one physician to another and in each instance was labeled "essentially neurotic." She was found to have a malignancy which later caused her death. This case impresses us with the importance of divorcing ourselves from preconceived notions. Each patient demands and deserves a thorough examination.

SUMMARY

To summarize briefly we have attempted in this paper to stress several important points two of which we should like to reiterate. The first the

necessity of a thorough survey of the patient, is generally accepted, if not practiced. The second, the use of drugs in psychoneurotics, is neither generally understood nor accepted. We have tried to show that there need be no taboo on drugs used with reason, that they are very helpful and that they are often of more psychotherapeutic value than other more frequently employed measures. In our study, we have seen a varied assortment of reaction types derive striking benefit from the temporary and rational use of drugs to relieve symptoms. We have refrained from making any statistical report at present because investigations of this nature do not easily lend themselves to mathematical arrangements. At present we simply bring forth the fact that in a large series of cases with more or less "nervous" etiologic factors the results obtained are better when a practical psychotherapy includes in addition to the usual measures (reassurance, superficial analysis, physiotherapy, rest, massage, exercise, occupational therapy) the use of drugs to relieve symptoms. If drugs are used sensibly we need not fear that they suggest organic disease and thus give the patient a reason for complain-

ing. However, we realize that this method is not applicable to all reaction-types. That there is a large group of cases where the mechanism of the reaction must be explained is agreed. On the other hand, it is a well recognized fact that the mental effect of a complete examination with an explanation of the condition and reassurance results in a "cure" in a large number of cases. As Lyon¹⁰ has aptly stated "By improving our methods of total diagnosis of a patient we thereby improve our chances of appropriately treating that patient from many angles instead of his chief major disease alone. The thoroughness of the total treatment is often the real secret of success."

We have introduced the term gastro-psychiatrist. The temperamental fitness of this individual differs greatly from the average psychiatrist or gastro-enterologist. He stresses neither the "whole" of the former, nor the "part" of the latter. He takes both into consideration *equally* and does not hesitate to cure the part while treating the whole. Not every gastro-enterologist and psychiatrist is suited for this specialty, they may practice it but not with all the attainable success.

REFERENCES

- ¹BLAND-SUTTON, SIR JOHN. The psychology of animals swallowed alive, *Brit Med Jr*, 1925, 11, 104.
- ²REYNOLDS, G. P. The etiology of psychoneuroses encountered in the practice of internal medicine, *New Eng Jr of Med*, 1930, ccciii, 312.
- ³RUGGLIS, ARTHUR H. Psychiatry's part in preventive medicine, *Ann of Int Med*, 1929, 11, 366.
- ⁴OVERSTREET, H. A. About ourselves. Psychology for normal people, 1927 Norton, N. Y.
- ⁵ALVAREZ, W. C. Nervous indigestion, 1930, Hoeber, N. Y.
- ⁶OLIVER, J. R. Fear, 1927, MacMillan Co.
- ⁷JELLIFFE, S. E. What price heading? A fragmentary inquiry, *Jr Am Med Assoc*, 1930, xciv, 1393-1395.
- ⁸DUBOIS, P. The psychic treatment of nervous disorders, 1905. Funk and Wagnalls Co., N. Y.
- ⁹ALVAREZ, W. C. Auto-intoxication, *Physiol Rev*, 1924, iv, 352.
- ¹⁰LYON, B. B. V. Non-surgical drainage of the gall tract, 1926, Lea and Febiger, Phila.

The Prestige of the Internist*

By MILES J. BREUER, M.D., F.A.C.P., *Lincoln, Nebraska*

INTERNISTS who are working in well-developed medical centers, on a basis either of referred work or of institutional work, are not frequently confronted with problems like the cases mentioned below. But from seventy-five to ninety per cent of the internal medicine of this country that is waiting and crying to be done conscientiously and scientifically, exists and awaits among the masses who do not have access to modern medical centers, whose medical conceptions are from fifteen to fifty years behind the forefront of modern medical thought, and who do not even know what an internist is. They do not understand the character of service involved in an "examination" as an internist means the word, have no idea of what a diagnostic study consists or what it can do for them. They just want a doctor. They came directly to the internist, and he must educate them to evaluate his services, or to be referred to other specialists.

Case 1, J. H., aged 55, traveling salesman, called the writer into his home on a number of occasions for the relief of acute abdominal pain. The principal therapeutic measure to which the pain responded was rest. On several occasions I advised this man that there was a possibility of the existence of a circulatory lesion not apparent to the type of examination that was possible

on an emergency visit, warned him of the danger that might result from its neglect and urged him to have a proper diagnostic study. He agreed with this, until it occurred to him to ask what the cost would be. When told of the probable cost of the necessary study and observation, he backed away in dismay. On several occasions he was willing to go to a hospital and be operated on, at a cost of from four to six times as much as the diagnosis would have cost, it took some rather firm dissuasion to convince him that he did not have a surgical lesion. After he found what the proposed examination might cost, he was very resentful and did not call me any more. One day he was found dead in his car, and the autopsy showed coronary stenosis.

Case 2 was seen in connection with a visit to a colleague in a neighboring city. A thin, pale young woman came to him requesting some medicine for her kidneys because of a backache. He explained to her the need of a thorough diagnostic study in a case like hers, and was also met with the question of the probable cost of such a study. The lady did not return to him, but we happened to see her about a week later when she was brought into a hospital clinic, paralyzed and anesthetic from the waist down and with sphincters paralyzed. She had gone to a chiropractor and paid him in advance for a series of treatments a sum not substantially different from the one estimated by the internist as the approximate cost of an examination. Further examination showed that she had tuberculous caries of a vertebra with fracture and compression of the cord.

As a multiplication of cases like the above could demonstrate the American public is not yet conscious of the

*Received for publication March 2, 1931.

internist as a new and different figure in medicine, who, on the one hand has a distinct type of service to offer differing considerably from "just going to a doctor and getting some medicine", and on the other hand who works under such conditions that there is a standard of expense connected with his services which also differs markedly from just "going to a doctor"

This lack of appreciation of the internist's function is not limited to the lay public. Just recently I received a friendly visit at my office from a man who ranks high on the surgical staffs of two hospitals and who has made a name for himself in a special field of surgery. I was showing him the records of a certain case, which at first had been diagnostically obscure, and afterwards had proved interesting enough to merit a thorough clinical study. He waved away my pile of records. "What do you want to do all of that for?" he asked in perfectly sincere deprecation, "Why don't you come right to the point?" His attitude is typically illustrative of that which I have found on the part of many medical men in our community which has the reputation of being a progressive one.

The writer does not believe in emphasizing the economic or business side of medical practice, and does not wish this article to be construed as a plea for some plan of bringing up the fees of internists. It is rather the expression of a desire to suggest the need of educating the public to understand the function of the internist, for the sole purpose of enabling the internist to function prop-

erly, and for no one's ultimate greater benefit than that of the public itself.

In this community, which is quite like ninety per cent of the rest of the United States, dentists and surgeons have already educated the public to a proper evaluation of their function, and to an acceptance of their standards of remuneration. The average man admits that the surgeon is perfectly justified in receiving a minimum of \$100 to \$300 for an operation. But, if someone should tell this same average man that the internist exercises quite as much skill and ability, assumes quite as much responsibility and that his services are of quite as much importance and value to the patient as in the case of the surgeon, he would be dubious and skeptical. He does not know enough about what an internist does, to form an intelligent opinion. And therefore, when an internist charges him a fee on a basis analogous to that of the surgeon or the dentist he is indignant and thinks he is being unjustly treated.

The reason for this is twofold. On the one hand the surgeon and the dentist have educated the public. Time and custom have succeeded in producing a willing acceptance of the situation. The public is reconciled to the cost and believes in the value of the service, and the surgeon and the dentist continue to develop their knowledge and their technic on a reasonably remunerative basis. On the other hand, there is a popular appeal about the accomplishments of surgery that is lacking in the humdrum, plodding procedures of internal medicine.

The public has a very poor knowledge and appreciation at the present time of some of the remarkable things that are being accomplished by internal medicine. Only a limited number of lay individuals are aware of the diagnostic marvels that our specialty has produced and of the therapeutic miracles that it is working. If the dissemination of such knowledge is left to the usual natural processes, it will be twenty years before the importance of electrocardiography and the magic of insulin are as much of a byword in the home as is appendectomy. Nor does the general public have any idea of the overhead expense involved in the diagnostic and therapeutic methods connected with internal medicine. Omitting entirely the consideration of the time and expense required on the part of the internist to acquire the necessary ability, what average layman has any idea of the overhead factors entering into the study of, for instance, a case with chronic epigastric pains and a loss of physical capacity, of the time and expenditure of lawyer-like skill necessary to extract the indispensable history, of the expenditures for laboratory work, the basal metabolic rate, the electrocardiogram, the x-ray, and the assistance of skilled technicians? The bill for a study of this sort stirs up the common man's resentment, because he cannot see what he has gotten for his money. Nothing illustrates this point better than the requests of many of these patients that they might keep their x-ray films, a desperate attempt to salvage something concrete and ob-

jective as a symbol of what they get for the money they have paid out.

This attitude, of course, makes the work of an internist difficult. Naturally, in response to it he makes some concessions. Either he omits work that ought to be done, or he does without charge work for which he ought to be paid. Either course handicaps the freedom of his scientific activities, unless he is fortunate enough to be practicing among a wealthy clientele, and this article is being written about the seventy-five or ninety per cent of internists and near-internists who are not so situated. From the very beginning of the study of such a case the internist feels under constraint, he knows that a financial argument is coming, and the thought interferes with the proper freedom of his efforts. It is not a question of whether or not the internist makes money. It is a question of providing him with the opportunity to study his cases adequately under a condition of affairs where the work must pay for itself. Under the present social organization most of our internal medicine is being done by men or groups who are not endowed and have no independent source of income. If the patient does not pay for the work, in the total summing up it cannot be done. Yet in all conscience it ought to be done. Therefore, the work must command adequate fees.

There is no other solution of the question than the education of the public, since most of us admit that the socialization of medical practice is a vague conception and far away from

us just now The public must be trained to recognize that an "examination" or a diagnostic study is quite as concrete and valuable a service as a surgical operation, in many cases comparably difficult and expensive

How can the public be educated?

First by that constant educational work that is being done by the individual practitioner, in personal contact with his patients After all, the doctor is today more of a teacher than a medicine man, and of no type of practitioner is this more true than of the internist

Secondly, writers from among our ranks should present the matter properly to the public through the common literary channels The procedures and accomplishments of internal medicine, the importance and difficulty of modern diagnosis, should be discussed for the popular medical reader The writer of this paper has been doing his best in that direction in the limited sphere in which his writings appear

Thirdly, the organized efforts of internal medicine should be consciously directed at the problem Every convention at which internists

gather ought to organize one meeting of its period which is open to the public for the adequate presentation of these matters to laymen

Beyond the application of the methods of modern efficiency to essential phases, the writer does not believe in any propaganda to build up the business side of our profession But, as long as the work of the internist must be self-supporting, nothing but the efficient application of modern methods of thorough and complete diagnostic study to all cases that require it, is going to meet the ideal of an adequate service to the public on our part Only a relatively small proportion of the cases that need this service, is getting it today Internal medicine is not as yet properly organized to deliver it as surgery is being delivered Yet, without modern diagnostic study of difficult and obscure conditions with a view to relief, and without the efficient recognition of early stages of serious diseases with a view to prevention, we are back in the dark ages of medical practice, and are failing to bring to the public the full benefit of modern scientific medical progress

Editorial

ON THE "CAUSE" OF CANCER

There is no dictum of medical import more commonly in the mouth of the layman than that the 'cause' of cancer is unknown. Lawyers make unfair use of it in compensation cases and the presiding judicial officer falls readily into the same trap. The medical witness is asked if he knows the cause of cancer and he modestly replies in the negative. He is then asked if *anyone* knows the cause of cancer and the usual answer is that as far as he knows the cause of cancer is not known. The questioner then makes his point by asking if, since the cause of cancer is not known, it is not just as probable in the case in question that cancer was due to such and such a factor as to anything else, and the witness gives a feeble and unwilling assent, although his best judgment tells him that it was highly improbable that any causal relationship existed.

The difficulty lies in the form of the question itself. The cause of disease is always complex. It does not tell the whole truth to say that the cause of tuberculosis is the tubercle bacillus. Not only does the more immediate physical and humoral constitution of the host determine whether the disease is to develop, but the entire phylogenetic experience of the two interacting organisms lies back of that form of abnormal life and abnormal living that constitutes tuberculosis. Innumerable

homely examples of the difficulty inherent in the form of the question can be found in everyday life. It is as though one had asked the cause of an elephant. In answer to such a query the keeper might think of the supply of provender which had been consumed during the long years of growth from birth to maturity, the geneticist of the union of the male and female reproductive cells with their intricate apparatus for the transmissal of unit characters, and the evolutionist of the millions of years of trial and error and success which have given to the elephant the huge bulk, thick skin, prehensile trunk and large ears which are part of his successful adjustment to his native habitat. But back of all this, and yet a part of it, as the chief cause of all, is life itself. It is equally true that life is a cause of cancer for the problems of neoplasia are the problems of *living* tumor cells descended from *living* body cells. Thus the question as to the cause of cancer is difficult and in a sense impossible to answer because its simplicity makes it profound.

Much is known, however, about factors which are concerned with the development of cancer and in one sense it may be said that the cause is known for the experimental pathologist can produce cancer at will. In suitable species of laboratory animals malignant neoplasms may be made to arise

de novo The lines along which this success has been attained point the way toward a classification of the known carcinogenic factors in man. On the one hand carcinoma can be produced in suitable laboratory animals by selective breeding, and on the other by the application of various extrinsic agents, as exemplified by the historical induction of carcinoma of the stomach of the rat by Fibiger through feeding cockroaches containing a nematode worm (*Spinoptera neoplastica*), and of the ear of the rabbit by painting with tar (*Yamagita*), brilliant successes of the greatest significance which in more recent years have been paralleled by various other workers using several diverse procedures. Thus the known factors productive of neoplasms fall into two main groups, one containing those which are inherent or developmental, and therefore peculiar to the individual, and the other made up of the *extrinsic* agents. The first of these groups has in turn two aspects. It must be divided into those factors which are disturbances of development in the morphological sense, *embryonal*, and those which are inherent in the genetic complexion of the individual, *intrinsic*. Thus it will be seen that the embryonal factors are developmental, the intrinsic factors are inheritable and the extrinsic factors are environmental.

The conception of an *embryonal* factor in the causation of neoplasms is of long standing (Cohnheim) and the list of tumors dependent in one way or another upon developmental defects such as the misplacement of simple or complex tissues, inclusion of tissue elements or even detached blastomeres

(included twins), and the persistence of embryonic structures into post-fetal life, is constantly increasing. Many varieties of new growths, both benign and malignant, have their origin upon such a basis. The teratomas of testis and ovary, hypernephroma, adamantinoma, chordoma, the mixed salivary gland tumors and many others thus arise. Yet it is equally true that many of the most common forms of carcinoma such as those of the lip, gastrointestinal tract and uterus cannot be thus explained.

The *intrinsic* factor stands in the forefront in the minds of many investigators today. Two great lines of evidence have supported it, the study of human inheritance as shown by certain so-called 'cancer families' (recently discussed in the ANNALS*), and the results of animal breeding experiments (Slye, Little, Lynch and others). The geneticists may differ among themselves as to the mendelian implication and interpretation of their results but there can be no doubt that under the conditions of the experimental laboratory the predisposition to the development of neoplasms can be bred in or out at the will of the trained investigator. Nor should it be expected that precise mendelian ratios will appear in such experimental series for the intrinsic factor is apparently a predisposing one only and the simultaneous operation of other factors must not be forgotten. There is some reason for believing that the intrinsic factor may be inherited in varying degrees of intensity.

*WARTHIN, A. S. Heredity of carcinoma in man. Ann Int Med, 1931, 11, 681-696.

That many *extrinsic* factors are carcinogenic has long been recognized. Chimney sweeps' cancer of the scrotum, the kangri cancer of the shepherds of Tibet, the more recently recognized mule spinners' cancer and, within our own profession, the many examples of carcinoma of hands and face among the earlier roentgenologists have provided ample proof. These are but a few of the many occupational, accidental and experimental examples of the effect of such extrinsic agents. Mechanical, thermal, chemical and radio-active forces are all found in the list. Here, also, are examples of chronic infection providing the instigating factor, but only through such mechanisms as chronic irritation and exaggerated response to injury does infection cause cancer. There is almost complete agreement among investigators that there cannot be a specific extrinsic living organism, infection with which causes cancer. There are important theoretical objections to such an etiology that cannot be entered into here. It is significant that there is no proved example of the transfer of a neoplasm from patient to nurse, doctor, or to any member of the patient's family. But chronic inflammation due to infection, with excessive reparative proliferation such as may be associated with lupus, or at the mouth of a sinus or the border of an ulcer, may provide the extrinsic stimulus. It is from the field of occupational medicine that much of our knowledge of extrinsic carcinogenic factors has come. The list includes soot tar, pitch, creosote, shale oil, petroleum, arsenic, aniline dyes, anthracene, radium, roentgen-rays, sunlight, burns

of thermal, electrical and chemical origin, and repeated mechanical trauma.

The relative potency and the mode of interaction of the developmental, the intrinsic and the extrinsic factors we know relatively little about, although evidence of value in this respect is accumulating. For purposes of illustration and discussion a mathematical form is of use. If D represents the developmental (embryonic) factor, E the extrinsic factor and I the intrinsic factor, the following equations should be true:

$$(I) \quad I + D + E = \text{cancer},$$

$$(II) \quad I + E = \text{cancer},$$

$$(III) \quad I + D = \text{cancer}$$

Since both human family histories and animal breeding experiments include strains in which practically every individual succumbs to a malignant neoplasm it seems highly probable that if the intrinsic predisposition is of a certain degree of intensity or combined with a certain organ predisposition either no extrinsic factor is needed or the ordinary minor environmental traumata may assume that role. The origin of cancer in such a case may be expressed by the equation:

$$(IV) \quad I = \text{cancer}$$

It is not so clear whether or not cancer can ever develop in the absence of the intrinsic factor. That certain pioneer roentgenologists daily and many times a day placed their hands before the fluoroscope to test the efficiency of their tubes and never developed cancer in spite of such protracted and intensive exposure may be due to the fact that they lacked the intrinsic predisposition.

If so the equation

$$(V) \quad I = \text{no cancer}$$

should be accepted as true. It might be a fruitful research to compare the family histories of the x-ray workers who developed cancer with the family histories of those who did not. If the intrinsic factor is necessary under such circumstances, may it not be true also, that

(VI) $D = \text{no cancer,}$
and (VII) $D+E = \text{no cancer?}$

Of this there is, as yet, no proof.

A brief survey of present opinion of the cause of cancer indicates that, after

all, much has been accomplished and much is known. Members of the medical profession will do well to present such material to intelligent laymen and thus aid in dispelling the popular opinion that cancer research has reached an *impasse*. As Woglom put it not long ago, one need only ask a medical man whether he would rather have a carcinoma now, or thirty years ago, to learn whether there has been any progress in our knowledge of the cause, prevention, diagnosis and treatment of cancer during that period.

Abstracts

Blood Cultures and Focal Infections An Experimental Study with One Hundred Healthy Adults By GORDON C CAMERON, C A RAE and GEO N MURPHY (Canadian Med Assoc Jr, 1931, xxv, 131-134)

Although it is generally assumed that the blood-stream of the healthy animal is normally free of bacteria there is much evidence, however, to indicate that pathogenic organisms do invade the blood-stream without necessarily producing disease. This is indicated by the frequent development of staphylococcal osteomyelitis following forms of trauma which could not effect the introduction of organisms. The subjects used in this investigation were presumably healthy young men who were interrogated as to present health and previous experience with disease. Inspection of the nose, throat and ears of each was carried out, as well as a detailed examination of the teeth with complete x-rays. A 20 cc sample of blood from each subject was incubated with 180 cc of beef heart infusion broth. These cultures were examined daily but were opened only after two weeks and four weeks of incubation. Of the 100 cultures, 81 remained without growth. Among the 19 showing growth it seemed certain that 12, and possibly 13, were contaminated. The remaining 6 showed growth of organisms believed to be derived from the blood. Four of these were characteristic of *Staphylococcus aureus* and the other two were "diphtheroids". Although there were 25 individuals in the group with x-ray evidence of apical disease of from one to four teeth, not one of the six positive cultures came from this group. One of the subjects who yielded a culture of *S. aureus* had a mucopurulent discharge from the right nostril, partial right nasal obstruction, a dim right antrum, enlarged tonsils and enlarged cervical nodes. The others were free of abnormalities which might be interpreted as disease except that two had a pustular acne on the back. While

aware that the method used might fail to demonstrate certain of the more dependent parasitic organisms, it was chosen in order to permit speed and simplicity in manipulation.

Metastatic Tumors in the Thyroid Gland By RUPERT A WILLIS (The Am Jr of Path, 1931, vii, 187-208)

In cases of systemic hematogenous dissemination of malignant tumors, the embolic influx into the various tissues must be proportional to their respective arterial blood supplies, yet such richly vascular organs as the intestine, spleen and thyroid gland are relatively infrequent sites for secondary growths resulting from hematogenous spread. Taking the total weights of the liver and thyroid to be 1500 and 25 grams respectively, it appears that the thyroid actually receives about one-half the volume of arterial blood received by the entire liver. Yet, while the liver is very frequently the seat of metastases derived from the systemic blood stream metastatic growths in the thyroid gland are unusual. The author collected and reviewed the records of 47 examples of metastatic thyroid growths, and added 10 cases personally observed. He concluded that secondary tumors occur more frequently in the thyroid than they are generally recognized partly due to failure to make thorough examination of this organ in doing autopsies upon the bodies of those dying of malignant disease. There are good grounds for believing that different tumor types possess different intrinsic capacities for establishing metastases in the thyroid and that melanomas and lime carcinomas are most potent in this respect. There is strong evidence that areas of abnormal thyroid tissue such as adenomas are predisposed to the establishment of metastatic neoplasms and that this predisposition depends on chemical or metabolic rather than on vascular changes in the altered tissues.

This predisposition on the part of pre-existing abnormal areas appears especially in connection with the metastases of neoplasms having relatively little tendency to colonize in the thyroid gland

The Blood Sugar of Normal Fasting Persons By B Y GLASSBERG (Proc Soc Exp Biol and Med, 1931, xxviii, 889-893)

The blood sugar values recorded generally in the literature represent the sum of the sugar and non-sugar reducing substances present. Somogyi has perfected a simple method of precipitation with zinc salts whereby, together with the blood proteins, the reducing non-sugars also are precipitated and thus filtrates are obtained that contain no appreciable amount of reducing substances other than sugar. Using such zinc filtrates, true sugar values are obtained in a single determination by any of the titrimetric or colorimetric methods in general use. The author determined the fasting true blood sugar in 100 normal adults, 50 men and 50 women. Samples were taken before breakfast, at least eight hours after the last meal. Somogyi's microtechnique for zinc precipitation combined with the Shaffer-Hartmann method was employed. Blood was obtained by puncture of the finger tip, the hand having been previously warmed in a basin of warm water. It was determined that capillary blood may properly be substituted for venous blood in determining the sugar of fasting individuals and that repeated squeezing of the finger to obtain successive samples did not modify the result through the admixture of other tissue fluids. The fasting true blood sugar of 50 men and 50 women was found to be between 70 and 95 mg per 100 cc of blood, with an average of 81.6 mg. The lowest blood sugar obtained was 70 mg, the highest 95.

Case of Pneumococcus (Type III) Meningitis Treated with Potassium Permanganate

Recovery By MAX H WEINBERG (Jr Nerv and Mental Dis, 1931, lxxvii, 38-45)

The very serious if not hopeless prognosis in pneumococcus meningitis has justified the use of various drastic methods of treatment such as continuous drainage, cisterna magna punctures, lavage of the ventricles and the injection of various irritating substances into the subarachnoid space. Stimulated by the results obtained by Chester in the treatment of pneumonia, as reported in the ANNALS in 1929, the author used potassium permanganate enemata in a case of meningitis shown bacteriologically to be due to pneumococcus, type III. A cleansing enema is first given followed by 4 ounces of the standard solution advocated by Nott, which contains 2 grams of potassium permanganate to one and one-half pints of water. Such enemata were given every four hours. The patient should lie on his left side and remain so for at least twenty minutes to facilitate retention. In the case described the patient made a rapid recovery and was practically normal eleven days after instituting treatment.

Suppression of Strychnine Convulsions by Barbiturates By W T DAWSON and CHARLES H TART, Jr (Proc Soc Exp Biol and Med, 1931, xxviii, 917-918)

Barbital (diethyl barbituric acid), phenobarbital (ethyl-phenyl), nembutal (ethyl-secondary amyl) and pernocton (B-bromallyl secondary butyl) were all found to possess the life-saving antagonistic action to strychnine poisoning which Zervas and McCallum demonstrated for amytal (ethylisomyl barbituric acid). By starting the administration of these drugs with the onset of convulsions it was found possible to save the lives of rabbits which had received strychnine in an amount in excess of the certain lethal dose. Phenobarbital was much more effective than barbital when judged by the amount of the drug necessary to control convulsions.

Reviews

Sixty Centuries of Health and Physick The Progress of Ideas from Primitive Magic to Modern Medicine By S G BLAXLAND STUBBS and E W BLIGH With an Introduction by Sir HUMPHREY ROLLESTON xvi + 253 pages, 64 plates Paul B Hoeber, Inc, New York City, 1931 Price, \$5.00

As Sir Humphrey Rolleston puts it in his introduction to this book, what embryology is to the study of man's structure and evolution, history is to the comprehension of an art or science. Thus it is easy to understand why the study of the History of Medicine has recently attracted more and more attention both in and outside the ranks of the medical profession. The present work, however, is by no means a history of Medicine in the usual sense. Rather it is an account of the growth and progress, the evolution of ideas, having to do with the search for health and its preservation. The preventive idea thus receives special emphasis throughout. While of necessity certain names and dates must appear, the pages are not made to bristle with them and the reader cannot lose sight of the progress of the central theme as the way is marked from primitive medicine to Metchnikoff, Banting and Theobald Adrian Palm, oftentimes by quotations from original sources. The illustrations are very well reproduced as full-page plates and add much to the value of the book. While written for the layman with an interest in the development of medical science, it should make an equally strong appeal to the medical man himself. Here is a book which the doctor can recommend to his lay friends as giving an interesting account of the development of modern preventive Medicine. We quote from the final paragraph: "It is often said that the future of Medicine is in the laboratory. Doubtless this is true, but it is through the agency of the devoted and observant practitioner that Health comes with healing in her

wings. The problem will be to convey the knowledge gained in the laboratory to the one man who can put it to practical use.

The Doctor and His Investments Financial Policy and Technique for the Physician By MERRYLE STANLEY RUCKEYER, B. Lit. M. A., Financial Editor, Medical Economics and Dental Survey, Financial and Editorial Writer, New York American and Associated Newspapers, Associate in Journalism, Columbia University ix + 330 pages P. Blakiston's Son and Company Philadelphia, 1931 Price \$2.50 postpaid

The doctor is faced with investment problems quite unlike those of the average business man. He cannot provide for the future by turning his profits back into his business. Even if he practices this by improving himself through graduate study and travel that investment dies with him in fact becomes useless when his active work ceases. The doctor must invest as a method of self-pensioning as well as for the purpose of providing for his family. Physicians as a class are readily susceptible to the suggestions of insincere advisers and doctors' names figure largely on the sucker lists of security charlatans. Well-meaning acquaintances and grateful patients find the doctor a childlike and trustful listener to amateurish financial advice although he would be the last to select a medical consultant by that method. The book under review considers with sympathy and understanding the financial problems peculiar to the physician. The twenty-seven chapters are grouped in three parts dealing respectively with the Investment Policy for Doctors, Fields of Investment for Doctors and Fitting Investments to the Doctor's Needs. Throughout a thorough knowledge of medical economics is revealed particularly in such chapters as those which deal with equipping the doctor's office with the pros and cons of Medical Arts Publishing and

with financial set-ups ensuring a proper perpetuation of clinical groups. A suitable life-term plan, an annual financial health examination, a proper diversification and a healthy conservatism are subjects receiving emphasis. Finally, definite financial prescriptions are offered for concrete cases covering the needs of the bachelor physician, the doctor with a family and the retiring medical man. This book deserves the fullest commendation. It can render a valuable service to all members of the profession.

Practical Dietetics for Adults and Children in Health and Disease By SANFORD BLUM, A B, M S, M D, Head of Department of Pediatrics and Director of the Research Laboratory, San Francisco Polyclinic and Post Graduate School. Fourth revised and enlarged edition. xi + 380 pages. F. A. Davis Company, Philadelphia, 1931. Price, \$4.00 net.

This, the fourth edition of this work, differs from the preceding chiefly in the addition of a list of the chief sources of vitamins and a discussion of alkaline foods and diets. Detailed dietaries are given for healthy individuals of various types and conditions, as well as for those suffering from a variety of diseases. This book must prove of considerable use to the physician who is frequently called upon to give concrete advice, rather than broad suggestions, in dietary matters. The reader may grope, as does the reviewer, to learn why a spinster with impaired digestion is permitted to eat cauliflower but forbidden to eat cabbage (provided the mode of cooking is the same), or what difference in dietary value causes tongue muscle to be taboo for those who are encouraged to eat steaks, roast beef and roast mutton.

A Manual of the Common Contagious Diseases By PHILIP MOEN STIMSON, A B, M D, Associate in Pediatrics, Cornell University Medical College, Attending Physician, Willard Parker Hospital, Chief of Staff, the Floating Hospital of St. John's Guild, Chief of Clinic, Department

of Pediatrics, Cornell Clinic, etc. xvi + 353 pages, 2 plates and 40 text figures. Lea and Febiger, Philadelphia, 1931. Price, limp binding, \$3.75, net.

This manual was intended primarily as a clinical guide for medical students and internes but also includes the practical working directions needed by the nurse in charge of a patient with a contagious disease. It should be of great value to all practitioners and particularly to school physicians. Concisely written, it is also surprisingly complete. The diseases considered are diphtheria, Vincent's angina, scarlet fever, measles, rubella, whooping cough, mumps, chicken pox, vaccinia, epidemic meningitis and poliomyelitis. In addition there are chapters on the principles of contagion, serum reactions and the general management of contagious diseases. The size of the book is convenient and the binding durable and practical. This manual can be heartily recommended to those desiring a concise reference text on the common contagious diseases and their management.

Chronic Arthritis and Rheumatoid Affections with Recovery Record By BERNARD LANGDON WYATT, M D, F A C P, with the collaboration of LOUIS I. DUBLIN and foreword by DOCTOR J. VAN BREEMAN. ix + 166 pages. William Wood and Company, New York, 1930. Price, \$2.50.

A chapter on the incidence of rheumatic disease is followed by one on types and causes, the two occupying 34 pages. Preventive measures and early diagnosis account for the next 22 pages. The remainder of this book deals with therapeutic procedures, particularly diet and physical agencies. Herein lies its value, for specific suggestions free from narrow prejudices are to be found. The author is fully alive to the futility of dietary fads, and the question of focal infection is treated with commendable restraint. At the end a number of blanks are provided upon which the patient may record progress notes, this procedure having been found to be of considerable value in securing his intelligent cooperation.

College News Notes

At the recent meeting of the American Society of Clinical Pathologists in Philadelphia, Dr Walter M Simpson (Fellow), Dayton, Ohio, was chosen as President-Elect of the Society

Dr Austin B Jones (Fellow), Kansas City, Mo, was elected President of the Internist Club during the May meeting

A Dermatologic Clinic on "Erythema Induratum", held by Dr Ralph Bernstein (Fellow), Professor of Dermatology, Hahnemann Medical College of Philadelphia, was published in the July number of the Hahnemannian Monthly

Dr Harold L Amoss (Fellow), Durham, N C, has gone to Peiping, China, for a four months' stay, as Visiting Professor in the Peiping Union Medical College

At the meeting of the 6th District Medical Society of the State of North Carolina, held in Durham on June 18, Dr Robert L Felts (Fellow), of Durham, was elected President for the ensuing year

Dr Thurman D Kitchin (Fellow), Wake Forest, N C, President of Wake Forest College and Dean of the Medical School of Wake Forest College, was recently appointed to serve on the Commission for the Improvement of the Laws of North Carolina, provided by the last General Assembly

Dr Verne S Caviness (Fellow), Raleigh, N C, read a paper on "The Early Diagnosis of Pellagra" before the North Carolina State Medical Society's meeting during April. This paper was published in the July Issue of Southern Medicine and Surgery

Dr Caviness also read a paper on "Blood Pressure" before the Johnson County (North Carolina) Medical Society on June

Dr Samuel W Sappington (Fellow), Philadelphia, is the author of an article, "Death's Tune Table and Passing Remarks," which was published in the July issue of the Hahnemannian Monthly

Dr Clement C Fihe (Fellow), Cincinnati, Ohio, was one of the guest speakers at a recent meeting of the Bourbon County (Ky) Medical Society

The North Carolina Radiological Society was recently formed with the following Fellows of the College holding offices

Dr J K Pepper, Winston-Salem—President

Dr W T Ramey, Fayetteville—Vice-President

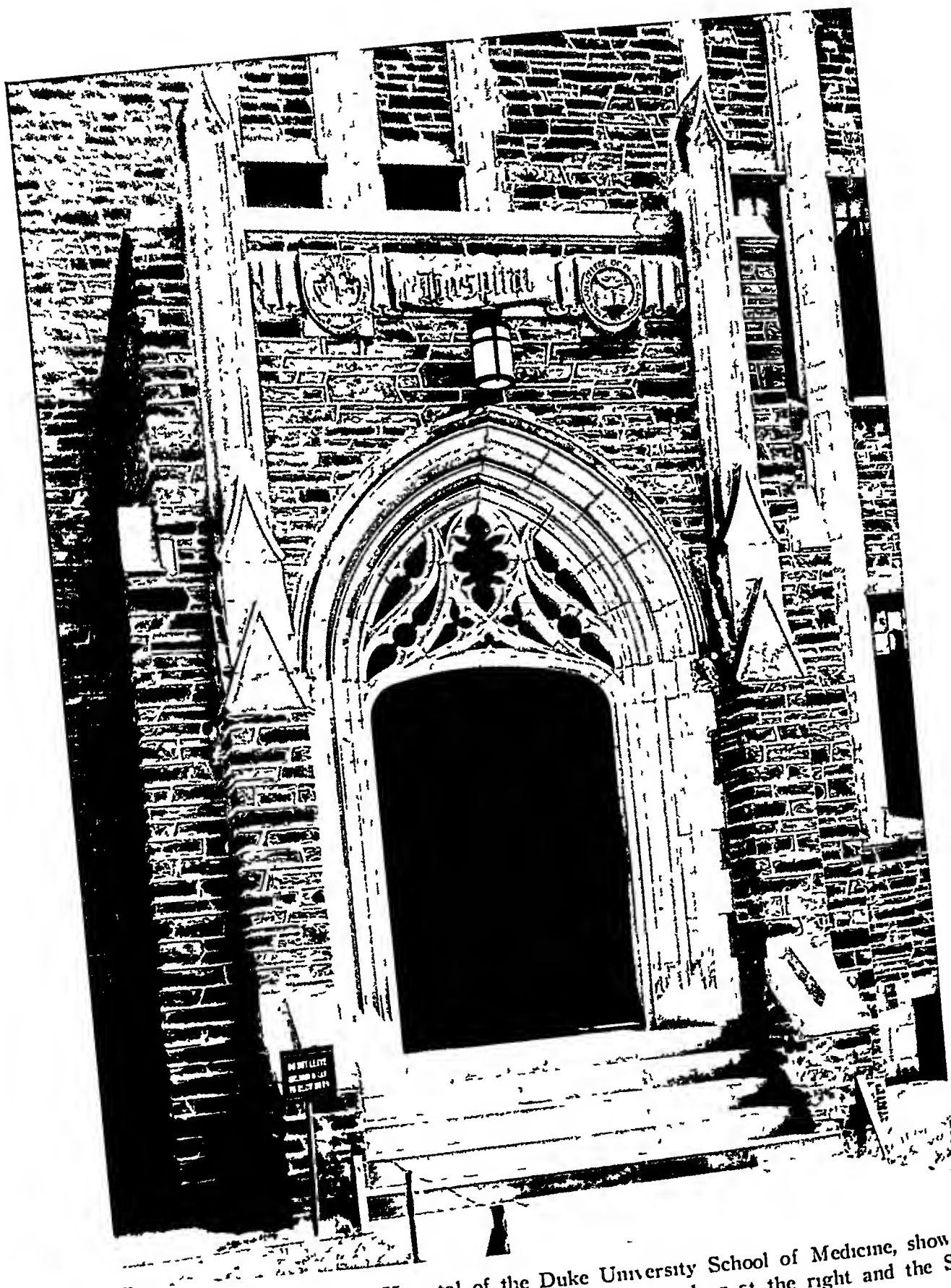
Dr Sylvester D Craig (Fellow), Winston-Salem, N C, was elected a member of the State Board of Health during the recent meeting of the North Carolina State Medical Society

Dr Thomas E Rogers (Fellow), Macon, Ga, read a paper on "Diagnosis and Treatment of Cardiac Arrhythmias" before the Sixth District Medical Society which met on June 24 at Indian Springs

Dr LaRue D Carter (Fellow) Indianapolis, addressed the Jay County (Indiana) Medical Society, July 2 on "Muscular Dystrophy"

Dr Thomas W Oberlin (Fellow) Hammond was elected President of the Indiana State Board of Health for two years during a reorganization meeting on July 2

Dr Henry G Rudner (Fellow) Memphis, Tenn, on June 18 addressed the East Mississippi Medical Society Philadelphia on "Symptoms of Colon Intoxication"



Main entrance to Duke Hospital of the Duke University School of Medicine, showing the Seal of the American College of Physicians above the door at the right and the Seal of the American College of Surgeons above the door at the left

DEDICATION OF THE
DUKE UNIVERSITY SCHOOL OF
MEDICINE
AND THE
DUKE HOSPITAL

ON
April 20, 1931

The new Duke University School of Medicine and the Duke Hospital were fittingly dedicated at Durham, N C, with an elaborate program. The erection of the School of Medicine and the Hospital marks another completed step in a far-reaching program conceived by Washington Duke and further advanced by his sons, Benjamin N and James B Duke, the latter of whom is directly responsible for the munificent gift founding the Duke University School of Medicine and the Duke Hospital in 1925. The cost of erecting the buildings for the School of Medicine and Hospital exceed four million dollars, leaving an endowment of six million dollars for maintenance. The architecture of all buildings is Gothic, there is but one architect for all the University buildings, resulting in a symmetry of design seldom carried out so fully in other American universities.

The wards in the new Duke Hospital have been named for distinguished physicians and surgeons, largely of the South, as follows: William H Welch, the only living physician for whom a ward is named, and who attended the dedication exercises, Sir William Osler, noted physician who made his home in Maryland for many years, Josiah Clark Nott, of South Carolina, Daniel Drake, of Kentucky, Walter Reed, of Virginia, William Stewart Halsted, of Maryland, Edmund Charles Fox Strudwick, of North Carolina, Crawford Williamson Long, of Georgia, Ephraim McDowell, of Kentucky, James L Cabell, of Virginia, J Marion Sims, of South Carolina, Francois Prevost, of Louisiana, and Henry Fraser Campbell, of Georgia.

Dr Wilburt C Davison (Fellow) is Dean of the Duke University School of Medicine. Other Fellows connected with the School are Dr Harold L Amoss, Professor of Medicine, Dr William DeB MacNider, Chapel

Hill, N C, Visiting Lecturer in Special Pharmacology, Dr P P McCain, Sanatorium, N C, Visiting Lecturer in Medicine.

Dr John E Greiwe (Fellow), Cincinnati, gave an illustrated lecture on "The Influence of the Peripheral Circulation" before the Darke County (Ohio) Medical Society on May 8.

The 84th semi-annual joint meeting of the Miami and Shelby County (Ohio) Medical Societies was addressed on June 4 by Dr Walter M Simpson (Fellow), Dayton on "Recent Developments in Undulant Fever".

Dr Byrl R Kirklin (Fellow), Rochester, Minn, was a guest speaker during the meeting of the Norfolk County (Va) Medical Society on June 1, the subject of his paper was "Gastric and Duodenal Ulcers".

Dr Jay A Myers (Fellow), Minneapolis, addressed the Washington Tuberculosis Association at Wenatchee, June 11-13, on tuberculosis problems.

Dr John T Strawn (Fellow) Des Moines, Ia spoke on "Gastric and Duodenal Ulcers" before the Madison County (Ia), Medical Society on June 8.

Beginning August 17, Dr Carl J Wiggers (Fellow), Cleveland, Ohio, conducted a vacation course on the principles and practice of electrocardiography at Western Reserve University School of Medicine.

Dr Henry H Turner (Associate) Oklahoma City, was among the speakers at the meeting of the Southeastern Oklahoma Medical Association on June 24. The title of his paper was "Ether Anesthesia".

Dr James S McMaster (Fellow) Birmingham, Ala addressed the Chattanooga and Hamilton County (Tenn) Medical Society July 9 on "Protein Quota in Health and Disease".

Dr Ray C Blankenship (Fellow) Madison, Wis, spoke on "Colitis" before the Ma-

inette-Florence County (Wis) Medical Society on July 9

Dr George B Eusterman (Fellow), Rochester, Minn, will address the ninetyeth annual meeting of the State Medical Society of Wisconsin, September 9-11, on "Carcinomatous Gastric Lesions Masquerading as Benign Ulcer"

A portrait, the work of Thomas C Corner, of Baltimore, of Major General Merritte W Ireland (Fellow) was unveiled in connection with a farewell reception given Dr. and Mrs Ireland, May 29, at the Army Medical Center, on the occasion of his retirement as Surgeon General of the U S Army The portrait will hang in the Administrative Offices of the new building of the Army Medical School

Col Matthew A Delaney (Fellow), Fifth Corps Area, Fort Hayes, Columbus, Ohio, beginning January 1, 1932, will be Assistant to Surgeon General Robert U Patterson of the U S Army, and will be advanced to the rank of Brigadier General Col Delaney was formerly Assistant Executive in the Surgeon General's Office During the World War, he served, first, in charge of Base Hospital No 10, and later as Liaison Officer with the British War Office He was the recipient of the Distinguished Service Medal, and also was decorated by the British Government

Col Charles F Craig (Fellow), after a service of thirty-three years, at his own request, has been retired from the Medical Corps of the U S Army He has accepted the appointment as Professor of Tropical Medicine and Director of the Department of Tropical Medicine at Tulane University of Louisiana School of Medicine

Col Craig is a graduate of Yale University School of Medicine He did postgraduate work in the Bureau of Science, Manila, and in the Rockefeller Institute for Medical Research From 1910-1911, he was Assistant Professor of Bacteriology at Yale University School of Medicine, from 1909-1922, Associate Professor and Professor of Bacteriol-

ogy, the Army Medical School, from 1926 to recently, he was Professor and Director of the Department of Laboratories and Preventive Medicine at the Army Medical School During the World War, he received the Distinguished Service Medal

In addition, Col Craig served four years as Commanding Officer of the Central Department Laboratory, Fort Leavenworth, Kansas, one year in charge of the Departmental Laboratory at El Paso, Texas, and four years as Medical Inspector in Hawaii

TULANE ESTABLISHES NEW DEPARTMENT OF PREVENTIVE MEDICINE

Announcement has recently been made that Tulane University of Louisiana School of Medicine has established a new Department of Preventive Medicine in connection with "the Commonwealth Fund of New York through which the University will participate in the rural health program recently initiated in Mississippi by the fund An annual appropriation of \$25,000 has been allotted by the fund to the School of Medicine to establish the new department and to encourage attention to preventive medicine in other clinical departments Five free scholarships have been established for undergraduate medical students from Mississippi, providing the student with \$1,200 a year for four years, with the requirement that after graduation he shall practice at least three years in Mississippi In addition, fifteen practicing physicians will be sent each year to Tulane for four months' graduate work Their tuition and transportation to and from New Orleans will be paid by the fund, and they will be allowed a monthly stipend of \$250" The arrangement with Tulane is said to be similar to that made with Harvard University Medical School for practitioners of Massachusetts

Acknowledgment is made of the following gifts of reprints and books by members to the College Library

Dr Oscar W Bethea (Fellow), New Orleans, La —4 reprints

Dr Orville H Brown (Fellow), Phoenix,
Ariz —11 reprints

Dr John L Chester (Fellow), Detroit,
Mich —1 book, "Rheumatic Fever—A Heart
Disease "

Dr Edward E Cornwall (Fellow), Brook-
lyn, N Y —1 reprint

Dr Oswald E Denney (Fellow), Carville,
La —12 reprints

Dr J L Goforth (Fellow), Dallas, Texas
—10 reprints

Dr George R Herrmann (Fellow), Gal-
veston, Texas—1 bound volume containing
sixty-two reprints

Dr Thomas Hall Shastid (Fellow), Du-
luth, Minn —1 reprint

Dr William H Strietmann (Fellow)
Oakland, Calif —1 reprint

OBITUARIES

DOCTOR LEONARD NAPOLEON
BOSTON

Dr Leonard Napoleon Boston (Fellow), a widely known physician of Philadelphia, died on July 4, 1931, at the age of fifty-nine years. Born in Shickshinny, Pennsylvania, on March 18, 1872, the son of Alfred H. and Bethiah (Bacon) Boston, a daughter of Rev. Septimus Bacon, who served in the War of 1812, Dr. Boston was educated at Huntington Mills Academy, Minneapolis High School and Atchison Commercial College, Atchison, Kansas. He taught school and attended college conjointly prior to entering the Medico-Chirurgical College, from which he was graduated in 1896. In 1895 Dr. Boston was graduated from the Philadelphia School of Anatomy with highest honors, in 1902 he received the honorary degree of A.M. from Ursinus College.

Two years after taking his medical degree, Dr. Boston became the Bacteriologist to the Philadelphia General Hospital, a position he held for six years. In 1901 he was appointed Bacteriologist of the Ayer Clinical Laboratory, Pennsylvania Hospital. He was Director of Clinical Laboratories at the Medico-Chirurgical College from 1901 to 1905. In 1906 Dr. Boston was appointed Director of the Clinical Laboratories of Research of the American Hospital for Diseases of the Stomach and soon thereafter became Pathologist at the Frankford Hospital. One year previously (1905) he was married to Miss Caroline Crandall of Westerly, Rhode Island.

Whilst Dr. Boston quite early directed his attention to bacteriology and

later pathology, he at no time forsook the clinical aspects of medicine for the laboratory side. For example, from 1897 to 1899 he was Instructor in Obstetrics at the Medico-Chirurgical College, Instructor of Medicine in the same school from 1899 to 1901, Associate in Medicine in 1904 and Adjunct Professor of Medicine from 1905 until 1912 when he was elected to a newly created chair of Physical Diagnosis, this professorship he continued to hold in the Medico-Chirurgical College, Graduate School of Medicine of the University of Pennsylvania, until 1817 when he became Assistant Professor of Medicine in the latter school, holding that position until his untimely death.

At the time of his demise, Dr. Boston was Professor of Principles and Practice of Medicine and Clinical Medicine in the Woman's Medical College of Pennsylvania, this important chair he had worthily filled since 1928. For a quarter of a century he was one of the physicians to the Philadelphia General Hospital. Here he gave much of his time and energy to bedside teaching—a form of instruction in which he excelled.

Dr. Boston was an author of note. In 1904 he published a text-book on "Clinical Diagnosis by Laboratory Methods." He was co-author with the writer of a text-book of "Medical Diagnosis," which appeared in 1911, and passed through three editions. He built up his enviable and well-earned reputation as practitioner, consultant, author and teacher, by his tireless energy and native ability, as well as high ethical ideals. Doubtless, he owed

some of his success to his unfailing courage and optimism

Toward his patients, he ever manifested deep human sympathy and at all times he radiated moral qualities which endeared him to his numerous friends. At social and professional gatherings, Dr Boston was a retiring figure, although upon being engaged in conversation was both entertaining and interesting, revealing an unusual fund of general and scientific knowledge. It is to be recollected, however, that his higher qualities of excellence emanated from the heart.

Dr Boston was the author not only of text-books, but of upwards of sixty scientific papers, many of which showed his bent for original laboratory and clinical observations. He held membership in many scientific societies and clubs, among which were the College of Physicians of Philadelphia, the Philadelphia County Medical Society, Medical Society of the State of Pennsylvania, the American Medical Association, American College of Physicians, Pathological Society of Philadelphia, the Society for the Study of Allergy, the Society of the War of 1812, the Sons of the American Revolution, the University Club and the Rotary Club of Philadelphia.

After he was graduated in medicine, Dr Boston settled in Philadelphia and took up general medicine. At the same time he became the office assistant to the writer for a period of seven years. During that period he manifested remarkable industry and loyalty performing every duty with absolute fidelity. His subsequent career was characterized by assiduous activity and devotion to the many duties devolving

upon him, until interrupted by the appearance of a serious cardio-vascular condition which, during the last four months of his life, incapacitated him from professorial and other professional duties. During this closing period of his busy life, coronary occlusion, most probably due to an atheromatous condition of the root of the aorta and the coronaries developed.

Surviving him are Mrs Caroline Crandall Boston, his widow, a daughter, Miss Barbara C Boston, a sister Mrs Myrtle B Eyler, and a brother Dr C A Boston.

(Furnished by J M Anders, M D M A C P)

DOCTOR JAMES P SCHUREMAN

Dr James P Schureman (Fellow) New Brunswick, N J died May 6 1931, aged, 51 years.

Dr Schureman graduated from Princeton University in 1901, and from the University of Michigan Medical School in 1905. He was one of the most prominent physicians in Middlesex County and was the first Fellow of the American College of Physicians in this part of New Jersey. He was highly respected by his colleagues and by the citizens of New Brunswick.

Dr Schureman was a man of charming personality, unselfish, most conscientious and devoted to the interests of his family and friends as well as patients. His family has been prominent in New Brunswick for nearly two hundred years. Dr Schureman was an Attending Physician on the Staffs of St Peter's General Hospital, Middlesex General Hospital and

Parker Home He was a Fellow of the American Medical Association, a member of the New Jersey State Medical Association and of the local societies He had been a Fellow of the American College of Physicians since 1925

Although interested in civic affairs

and a Trustee of the Anable School, Dr Schureman devoted practically his entire time to his professional work (Internal Medicine) and hospital affiliations

(Furnished by Frederick L. Brown, M D , F A C P , New Brunswick, N J)

Variations in Manifestations of Rheumatic Fever in Relation to Climate*

By WARFIELD T. LONCCOFF, M.D., F.A.C.P., *Baltimore, Md*

THE statement can frequently be found in textbooks and monographs that rheumatic fever is ubiquitous. This generalization (which is often attributed to Hirsch¹) can, however, scarcely be accepted today. Aside from the interest which has always been aroused by the seasonal incidence and familial occurrence of rheumatic fever, as well as the yearly variations in the severity of the disease there has recently been some attempt to study, more accurately than has been possible before, the geographical distribution of the disease. The matter is one of importance not only in relation to rheumatic fever but in connection with other diseases. It is now well recognized for instance that infections such as scarlet fever and diphtheria so common in the temperate zones are almost unknown in some tropical countries. The geographical distribution of pernicious anemia also, is very irregular. It is said to be almost unknown in China and Japan (Mills-)

My interest in possible climatological differences in the symptomatology

of rheumatic fever was awakened almost ten years ago on coming to Baltimore from New York. Arthritis was often the predominant symptom of acute rheumatic fever in the adult in New York and the one for which the patient called the physician or entered the hospital. Combined with the severe arthritis, or sometimes without severe arthritis, there was not infrequently observed acute severe, and sometimes fatal endocarditis, pericarditis, myocarditis, pleurisy and pneumonia.

In Baltimore on the other hand the acute severe arthritis so familiar in New York was rarely encountered in the wards of the hospital. In general though the disease seemed common in Baltimore it presented a somewhat different clinical picture appearing more insidious, less outspoken in its arthritic manifestations, not so fulminant in its severe forms but suggesting usually a chronic or relapsing progressive disease of the heart. In order to obtain more definite information on these points the case histories of patients with rheumatic fever treated during the last five years in the adult medical wards of the Johns Hopkins Hospital have been analysed.

*From the Medical Clinic, the School of Medicine, Johns Hopkins University and Hospital. Read at the Baltimore Meeting of the American College of Physicians, March 23, 1931.

It is difficult, as Newsholme³, who was interested in this question, found many years ago, to obtain accurate information regarding the regional distribution of rheumatic fever throughout the world. The statistics collected from hospitals by Faulkner and White,⁴ by Harrison and Levine,⁵ and by Seegal and Seegal⁶ indicate that rheumatic fever is commoner and more severe in the colder portions of the temperate zones than in the warmer portions. Seegal and Seegal also found that the incidence of rheumatic fever was greater from 1916 to 1918 than from 1918 to 1925. Excellent as these statistics are, they are based on diagnoses made in a variety of hospitals, and one cannot help but wonder upon what criteria the diagnoses were made. Do these statistics represent only those cases of rheumatic fever presenting arthritis, or do they include all cases of rheumatic fever? It is usually assumed that practically all cases of mitral stenosis are instances of rheumatic fever in the active, quiescent or healed stage of the disease. It is therefore very important in investigating the geographical distribution of rheumatic fever to know the regional distribution of mitral stenosis. Meleney and Kellers⁷ state that though rheumatic arthritis is rare in China, mitral stenosis is common. Harrison and Levine found mitral stenosis frequent in Boston, St. Louis and Baltimore, much less frequent in Galveston, Richmond and Oklahoma and rare in New Orleans. Wood, Jones and Kimbrough⁸ find rheumatic fever and rheumatic heart disease about half as common in Virginia as in Massachusetts. Clarke⁹

believes that rheumatic fever is almost unknown in natives in the tropics, defining the tropics as an area lying between 23° 28' North and South. He states that he did not see a single case of rheumatic heart disease among 150,000 hospital cases in Perak, Malay States. Coburn¹⁰ quotes Getz as stating that in the last 4 years only three unquestioned cases of rheumatic pancarditis have been recognized at autopsy at the Hospital of Santo Tomas in Panama. According to Coburn, rheumatic fever is extremely rare in Porto Rico. In about 500 autopsies studied by Dr. Lambert and Dr. Pappenheimer no gross or microscopic lesions of rheumatic fever were found. In a later series, however, two autopsies showing rheumatic pancarditis have been recorded.

The information, therefore, that is obtainable through published statistics and from such important personal surveys as that made by Coburn, goes to show that rheumatic fever, in all its forms, is exceedingly rare in the tropics, though rheumatic heart disease is not unknown in some tropical countries, whereas all the manifestations of rheumatic fever are common in the colder portions of the North and South temperate zones, where rheumatic arthritis is particularly prominent. In the intermediate and warmer regions of the temperate zones, rheumatic fever is certainly not recognized with as great frequency as it is in the colder regions. The geographical distribution, according to Coburn, corresponds to that of scarlet fever.

In analysing the cases at the Johns Hopkins Hospital rheumatic fever has

been considered as a generalized disease, and consequently there have been included in this category all instances of chorea, of mitral stenosis, of rheumatic pancreatitis and of rheumatic arthritis, whether they have been observed in the active, quiescent or possibly healed stages of the disease. In the majority of the cases there was some definite evidence of activity while the patient was under observation in the hospital wards. It may be seen from Table I that rheumatic fever is quite common in Baltimore, for 137 per cent of all patients admitted to the adult medical wards suffer from rheumatic fever. The cases of rheumatic fever, moreover, form a fair proportion of all autopsies, at least 166 per cent. The figures for

TABLE I
ADMISSION OF RHEUMATIC FEVER TO
ADULT MEDICAL WARDS
Five Year Period—Sept 1st, 1925 to Oct
1st, 1930

Total Admissions =	10385
Rheumatic Fever =	142
Admission Rate =	137%
Total Autopsies 1908-1929 =	8164
Total Rheumatic Carditis =	146
Per Cent Rheumatic Carditis =	16

the admission rate are a little higher than those given by Faulkner and White for the Peter Bent Brigham Hospital in Boston (Table II).

Since 36 of the 146 autopsies showed rheumatic heart disease in acute or subacute form, it may be inferred that the disease may occur in Baltimore as an acute and severe infection. The total mortality for the 142 cases was 16.2 per cent. Table III shows the age incidence at the

TABLE II
REGIONAL DISTRIBUTION OF RHEUMATIC FEVER
(Modified from Faulkner and White)

PLACE	Av Yearly Med Admis	Rheumat F (Chorea)	Per Cent
Johannesburg, S Africa	2906	169	5.8
Glasgow Royal Infirmary	2,655	126	4.74
Mt Sinai, N Y	1,641	58	3.6
Royal Prince H, Australia	1966	58	2.9
London Hospital	10,273	274	2.7
Univ Hosp, Iowa	1,537	38	2.4
P B B Hosp, Boston	2,480	31	1.3
J H Hosp, Baltimore	1,723	23	1.37
Univ Hosp, Omaha	760	5	0.7
Barnes Hosp, St Louis	1,358	65	0.47
Charity Hosp, New Orleans	5,349	28	0.4
Univ Hosp, Atlanta Ga	2,500	2	0.08

TABLE III
142 CASES OF RHEUMATIC FEVER

Age	Total Cases	Auricular Fibrillation	Heart Block	Bacterial Endocarditis	Deaths
0-20	49	3	0	3	13
21-30	40	4	3	6	7
31-40	33	12	6	2	8
41-50	14	11	1		3
51+	6	6		1	2
Total	142	35	10	12	23
Per Cent		25.3	13.4	8.5	16.2

time of observation, the occurrence of auricular fibrillation, the incidence of prolonged A-V time and the number of cases complicated by bacterial endocarditis. It is interesting to note that the proportion of patients with auricular fibrillation increases with the increase in age, and that bacterial endocarditis usually occurs in the younger individuals. The percentage of 1st, 2nd and 3rd degree heart block is small, but this is no doubt due to the fact that single electrocardiographic records were made in many instances. The figures show that delay in A-V conduction is also commoner in the younger than in the older patients, associated in all probability with the greater activity of the rheumatic process in the younger patients.

Males and females were almost equally affected, many more instances of rheumatic fever occurred in the white than in the colored race (Table IV). A careful analysis of the histories of these 142 cases and the condition on admission to the hospital discloses some interesting facts. Table V records the frequency with which various manifestations of rheumatic

fever occurred during the life of these patients before they were seen in the hospital. The past history shows that in 15 there was no history of any illness, simulating rheumatic fever and in 27, or 19+ per cent, there was no history of any rheumatic manifestation other than tonsillitis. There was a history of some form of arthritis without a history of cardiac disease in 37 patients, or in only 26+ per cent. On the other hand, cardiac disease is found to be remarkably common. In 14 cases there was a history of cardiac disease alone, and in 73 patients, or over 50 per cent, a history of cardiac disease either alone or in combination with some other manifestation of rheumatic fever. It is thus obvious that even in the histories of these patients cardiac disease is an important feature.

When one analyses the condition of the patients on admission to the hospital, the importance of cardiac disease becomes even more impressive (Table VI). Of the 142 patients, only 6 were admitted with arthritis alone and one with chorea alone. Of the entire number, 58, or only about 40 per cent, suffered with arthritis on admission, or during their stay in the hospital, while 135 or over 95 per cent, were admitted with cardiac disease or showed evidence of cardiac disease while in the hospital.

TABLE IV
SEX AND COLOR
142 CASES OF RHEUMATIC FEVER

Male	73	Female	69
White	59	White	55
Colored	14	Colored	14

TABLE V
HISTORY OF PREVIOUS MANIFESTATIONS OF RHEUMATIC FEVER—
142 CASES

No arth. ion chorea card	15	Cardiac alone	14
Tonsillitis alone	12	Arth. and cardiac	43
Chorea alone	5	Chorea and cardiac	2
Arthritis alone	34	Arth. chorea and cardiac	11
Arthritis and chorea	3		
Total arthritis no cardiac	37	Total cardiac	73

TABLE VI
RHEUMATIC FEVER—142 CASES, CONDITION ON ADMISSION

Diagnosis	No	Diagnosis	No
Arthritis alone	6	Cardiac disease alone	80
Chorea alone	1	Arthritis and cardiac disease	49
Arthritis and chorea	0	Chorea and cardiac disease	3
		Arthritis, chorea and cardiac disease	3
Total arthritis	58	Total cardiac disease	135

The observations upon these patients in hospital show quite definitely that many of them, though they gave no history of cardiac disease and though they were ignorant of the fact that they had cardiac disease, had had, nevertheless, cardiac disease probably for some years.

The figures thus emphasize the fact that rheumatic fever, as we see it, is essentially a disease of the heart, which may be preceded or accompanied by arthritis, often mild in character, by chorea, by tonsillitis, or occasionally by pleurisy, pneumonia, subcutaneous nodules and skin eruptions. During the acute stages the disease may be very severe or even fatal. Acute pericarditis occurred in 9 cases, acute pleurisy in 2, subcutaneous fibroid nodules were found in only 3 cases. Though many of these patients have died during the healed stage of the disease from the effects of the cardiac lesions or from such complications as bacterial endocarditis, at least 9 of the 22 autopsies showed that death was associated with some form of acute rheumatic carditis. The analyses which Dr Thayer¹¹ has made of the fatal cases of acute and subacute rheumatic fever show that fatalities during the acute and subacute stages of the disease are not very rare at the Johns Hopkins Hospital.

Table VII shows the forms of heart disease observed in the 135 cases. Al-

most all of these patients presented the signs of disease of the mitral valve. A comparatively large number also showed the signs of aortic insufficiency. In three cases the signs were those of aortic insufficiency alone, though it seems probable that mitral disease also existed in these cases. In a few instances myocarditis or chronic adhesive pericarditis was present without the signs of mitral disease.

TABLE VII
FORMS OF CARDIAC LESIONS
IN 142 CASES OF RHEUMATIC FEVER

Mitral stenosis and insufficiency	76
Mitral sten and aortic insuff	50
Aortic insufficiency	3
Myocarditis	3
Acute pericarditis	3
Total	135

DISCUSSION

In reviewing these histories of patients, many of whom I have studied in the wards, the fact becomes quite clear that rheumatic fever is practically as common in the hospitals of Baltimore as in the hospitals of Boston. The character of the disease is not precisely the same for arthritis in the severe form, is certainly not common in Baltimore and arthritis even in mild degree occurs in only a moderate proportion of cases. Cardiac disease on the other hand is extremely common and has been present in 95 per cent of the cases that we have studied. Patients are not often

seen in the florid stage of the disease, though severe acute rheumatic pancarditis is by no means unknown. As compared with the incidence of cardiac disease in other series of cases of rheumatic fever, the figures at the Johns Hopkins Hospital are rather high. Mackie¹² states that serious cardiac disease occurred, irrespective of age, in 68.3 per cent of his series of 393 cases of rheumatic fever, and that between the ages of 10 and 15 approximately 78.2 per cent of all cases presented evidence of cardiac disease during the first attack. Poynton¹³ found cardiac disease present in 70 per cent of 500 rheumatic children whom he examined. These figures are a high average for those found in the literature.¹⁴ At the risk of redundancy, then, it may be repeated that rheumatic fever, as seen in Baltimore, is essentially rheumatic carditis often of insidious onset, with comparatively mild acute exacerbations, but progressing none the less to a chronic deforming endocarditis with involvement of the myocardium and often of the pericardium, and resulting eventually in chronic invalidism and death. The carditis may be preceded or accompanied by attacks of arthritis, usually mild in character or by chorea.

The predominance of carditis in rheumatic fever and the insignificance of arthritis as a feature of the disease has been observed elsewhere. Meleney and Kellers have called attention to the fact that mitral stenosis occurs only a little less frequently in Peiping, China, than at St. Bartholomew's Hospital in London, and yet rheumatic arthritis is almost unknown in Peiping or in North China. Coffin¹⁵ points out that mitral disease is encountered in Ore-

gon with a frequency entirely disproportionate to the number of cases of rheumatic arthritis, and Houston¹⁶ in describing 88 cases of rheumatic fever which occurred during a period of four years amongst 115,213 general admissions to the Charity Hospital in New Orleans, emphasized the mild character of arthritic symptoms and the frequency with which cardiac disease occurred (51.1 per cent).

It seems possible, therefore, that rheumatic fever might be detected more frequently in the Southern States and in semi-tropical countries if the disease were regarded as one primarily of the heart, and if it were thoroughly appreciated that arthritis is an insignificant feature, an episode which may attract little attention or may be entirely absent.

CONCLUSIONS

The available statistics concerning the geographical distribution of rheumatic fever indicate that the disease is very rare or almost unknown in the tropics, and much less commonly observed in the warmer portions of the mid-temperate zones than in the colder portions.

In some regions where rheumatic arthritis is said to be rare, mitral stenosis is quite frequently observed.

At the Johns Hopkins Hospital in Baltimore the admission rate to the adult medical wards for rheumatic fever, in all its forms and in all its stages, over a period of five years was 1.37 per cent. The autopsy rate for rheumatic heart disease over a period of 21 years was 1.66 per cent. The disease, therefore, is comparatively common.

An analysis of 142 cases of rheumatic fever studied during this period

showed that symptoms or signs of cardiac disease appeared in the past histories of 50 per cent of the cases

Cardiac disease was present on admission to the hospital or was detected during observation in hospital in 95 per cent of these cases. Only 6 of the entire 142 cases presented symptoms and signs of arthritis alone, but in 77+ per cent arthritis, often of mild degree, occurred at some time during the illness for which they were admitted to the hospital

Rheumatic fever, as it is seen at the Johns Hopkins Hospital, is essentially

a disease of the heart frequently preceded or accompanied by arthritis often of mild degree, or by chorea. Severe acute arthritis is rarely seen but acute pericarditis and pleurisy are not very infrequent

It is suggested that the infrequency of severe acute arthritis, the great frequency of carditis and the comparative insidiousness of the disease during the acute and subacute stages renders the clinical picture of rheumatic fever somewhat different in Baltimore from that generally described for more northern sections of the United States

BIBLIOGRAPHY

- ¹HIRSCH, A. Handbook of geographical and historical pathology, London, New Sydenham Society, 1886, 3
- ²MILLS, C. A. Geographic or climatic variations in the death rate from pernicious anemia, exophthalmic goiter, Addison's disease and angina pectoris, Arch Int Med, 1930, xvi, 741
- ³NEWSHOLME, A. The Milroy lectures — The natural history and affinities of rheumatic fever, Lancet, 1895, i, 589 and 657
- ⁴FAULKNER, J. M., and WHITE, P. D. The incidence of rheumatic fever, chorea and rheumatic heart disease, Jr Am Med Assoc, 1924, lxxviii, 425
- ⁵HARRISON, T. R., and LIVING, S. A. Note on the regional distribution of rheumatic fever and rheumatic heart disease in the United States, South Med Jr, 1924, xvii, 914
- ⁶SIEGAL, D., and SIEGAL, B. C. Studies in the epidemiology of rheumatic fever Jr Am Med Assoc 1927, lxxxix, 11
- ⁷MILLER, H. E. and KILLICK, I. Mitral stenosis without rheumatic fever in North China, Arch Int Med, 1924, xxxv, 455
- ⁸WOOD, I. I., Jr. JONES, T. D. and KIMBROUGH, R. D. The etiology of heart disease, a clinical study of 623 cases with certain observations on race and climate. Am Jr Med Sc 1926 clxxviii, 185
- ⁹CLARK, J. T. The geographical distribution of rheumatic fever, Jr Trop Med and Hyg, 1930 xxxiii, 249
- ¹⁰COBURN, A. F. The factor of infection in the rheumatic state 1931 Williams and Wilkins Co., Baltimore
- ¹¹THAYER, W. S. Studies on bacterial (infective) endocarditis, Johns Hopkins Hosp Reports, 1926, xxi, 1
- ¹²MACKIE, T. T. Rheumatic fever. An analytical study of 393 cases of rheumatic fever and 80 cases of chorea, Am Jr Med Sc, 1926, clxxviii, 109
- ¹³POYNTON, F. J. Rheumatism in childhood, Practitioner 1913 xc 389
- ¹⁴LAMBERT, ALAN. The incidence of acute rheumatic fever at Bellevue hospital, Jr Am Med Assoc, 1920 lxxv, 923
- CABOT, R. Facts on the heart 1926 Saunders
- ROBIN, F. Der akute Gelenkrheumatismus, 1920
- HECHT, C. Akuter Gelenkrheumatismus. Handb der Inn Med v. Bergmann und Stuchlin 2nd ed. 1925 Vol I p 746
- KIM, C. G. The prognosis of acute articular rheumatism. Quart Jr Med 1914 vii 251
- ¹⁵CORLISS, T. H. The incidence of heart disease in the Pacific Northwest. Jr Heart Jr 1923 vi 99
- ¹⁶HOLSTON, A. N. Anderson's studies of rheumatic fever. Med Clin N Am 1928 xi 1379

Colonic Changes in Chronic Arthritis*

By W H DICKSON, M D , C M , F R C P (Can), *Toronto*

THE etiology and progress of changes in the colon so often noted in arthritis have been very great controversial points. Where many different opinions are held as to the cause of a condition and many methods of treatment advanced for the alleviation of the disease, it is evident a true understanding of the basic factors has not been reached. The roentgenological observations which we report here were noted on examination of patients suffering with chronic arthritis. The investigation was carried out by the permission of Professor Duncan Graham, and with the collaboration of Dr A A Fletcher of the Department of Medicine. These observations have proved certain phases in the interpretation of the colonic disturbances, and we believe have an important bearing on the evolution of the disease.

Goldthwaite and Brown¹ pointed out the frequent observation of enteroptosis in patients suffering from chronic arthritis, and believed the enteroptosis to be either constitutional or acquired from faulty body mechanism. Assuming these premises to be correct, he and his co-workers treated many cases of arthritis by the appli-

cation of belts, improvement of posture, and regulation of the function of the bowels.

Lane² defined stasis "as such a delay in some portion of the intestine, but more particularly the large bowel, as allows the absorption into the circulation of a larger quantity of toxic material than can be dealt with effectively". The delay, he remarked, is brought about by a mechanical alteration in the drainage apparatus. Among the many clinical manifestations due to colonic stasis, he particularly drew attention to arthritis. Lane stated that in early life colonic stasis is caused by abnormal distention of the bowel through too frequent feeding, or articles of diet of an unsuitable nature. Later in life it is brought about and accentuated by the erect posture of the body. He holds this posture causes a drag upon the principal points of support, tending to the promotion of bands and kinks at these points. These bands and kinks are evolutionary and not inflammatory. Proximal to these bands and kinks he states dilatation and stasis occurs.

Lane's theory of colonic stasis is combated by many observers. Bassler³ believes these bands to be physiological and that sagging of the colon does not necessarily mean colonic stasis. Daniel⁴ holds these bands to be

*Read at the Baltimore Meeting of the American College of Physicians, March 27, 1931

due to a localized peritonitis Keith⁵ does not accept Lane's idea and denies that bands or kinks produce delay in the food stream. In defense of his statement he submits his own theory. He has noted in the myenteric plexus, or rather intermediate between the plexus and muscular fibres, certain cells partaking of the character of nerves and muscle. This he calls nodal tissue because of its close resemblance to the nodal tissue in the heart. His suggestion is that irregularities in impulse conduction may occur in the nodal system of the colon, and cause stasis as in heart block. We have also noted marked improvement in colonic tone during spinal anesthesia and following a section of the lumbar sympathetic branches.

Jordan⁶ who long supported Lane stressed the roentgenological evidence of drags at the ligament of Treitz, kinks, and bands in the last part of the terminal ileum, the hepatic flexure, the splenic flexure and the sigmoid. These he states are evidenced by a constriction of the lumen of the bowel at the site of involvement, limitation of movement on forced inspiration, on palpation and with postural change. Jordan's investigation for years formed the ground-work for roentgenological study of the colon in colonic stasis and colonic dilatation.

Rae Smith⁷ recently discussed the relation of the pathology of the right lower quadrant to arthritis, paying particular attention to the blue thin-walled toneless cecum and has obtained relief following plastic operation upon the large bowel. He emphasizes the presence of constricting bands upon the ascending colon, believing the etiology

of the constriction to be due to faulty fusion in the last stage of migration, rotation and descent of the colon. As a result of the faulty fusion we have a *cecum mobile* and an ascending colon possessing a mesentery. He states "Given this faulty fusion we have the stage set for a long chain of events. Starting with the loss of tone due to advancing years or a long strain due to illness, we have a loss of the lumbar curve, that is the shelf on which the cecum rests. With the loss of the curve the cecum tends to prolapse. In an effort to correct the position of the prolapsing cecum nature starts the growth of a membrane at the site of the right colic artery on the mesentery side. This attaches the colon to the side wall by a reduplication of the peritoneum the colon is rolled and twisted pressure on the myenteric plexus results (here he evidently supports Keith's theory), a spasticity of the distal bowel results, with atony of the proximal portion, the cecum and the ascending colon."

Taylor⁸ collaborating with Smith minutely describes the technique used in the roentgenological demonstration of these changes, and in an illuminating manner gives his interpretation of the screen and film findings. We are heartily in accord with Taylor's findings. On many occasions have we demonstrated the cecum low in the pelvis atonic to boggy and on palpation have demonstrated a marked mobility raising the cecum at times to a point where it may be superimposed upon the splenic flexure. The deformity of the ascending colon also is often seen due to the membrane described by Smith, and the spastic distal

bowel is easily demonstrated. Occasionally at the six-hour examination the head of the meal will be present in the sigmoid, the colon from the site of the veil on the ascending colon to the sigmoid presenting the so-called "string type"

Our experience however has not allowed us to arrive at the same conclusions as Drs Smith and Taylor. Of the large number of our cases giving the roentgenological findings described by them, very few indeed presented any evidence of arthritis, nor were we able to elicit a history of any attacks simulating that disease. On the other hand, in the many definite cases of arthritis that it has been our

privilege to examine in collaboration with Dr Fletcher, very few indeed have shown changes analogous with those observed by Dr Taylor.

While it is the generally accepted theory that arthritis is as a rule secondary to some focal infection, the belief has been held to a degree that diet, or rather improper diet, has some relation to arthritis. Pemberton⁹ advised diets low in calories and restricted in carbohydrates, and my colleague in this investigation, Dr Fletcher,¹⁰ has stressed the use of diets high in vitamins and low in carbohydrates.

McGarrison¹¹ in his work on animals showed that atony of the colon



FIG 1



FIG 2

FIGS. 1 and 2 Miss C, aged 17. Pain and swelling of the metacarpal joints for ten years. During summer of 1928 arthritis developed in knees, ankles, and shoulders. No history of sore throats and no focus of infection found. Admitted to hospital September 29, 1928 with moderately severe arthritis of rheumatoid type and also aortic mitral valve lesions with moderate cardiac hypertrophy. Changes are shown which occurred in the colon over six weeks of dietetic treatment. Marked improvement in the arthritis occurred during this time.

can be brought about by diets deficient in vitamin B, and suggests that the disturbance of mobility and tone in the lower bowel might be of nutritional origin. Using these results of McGarrison as a basis, we attempted to repeat his work, using white rats as our subjects and making our observations by the use of the barium enema.

Normal rats, well nourished and fed upon a diet rich in vitamin B, were given barium enemas. After this examination a diet deficient in vitamin B was exhibited for several weeks, when a second enema was given. The diet was again returned to one high in vitamin B and a third enema administered in a month's time.

The colon underwent marked changes during the observation. The second examination showed the bowel elongated and very atonic, so atonic in fact that the pressure from the flow of the enema was great enough to rupture the colon, and the enema poured out into the abdominal cavity. The rats we were fortunate enough not to lose by this accident were at once placed on a diet again rich in vitamin B and further observation made in a month's time.

At the third observation the tone of the bowel had returned to normal appearance, and it was much shortened in its total length. In some of the rats it was difficult to demonstrate any difference between appearances at the first and at the third enema.



FIG. 3



FIG. 4

FIGS. 3 and 4. Mrs. D., age 44. Moderate degree of osteoarthritis on three occasions. Blood pressure 178/108. Picture shows changes which appeared in the colon during two months of dietetic treatment. Well marked improvement took place while on this treatment.

With this point before us, it was assumed that some of the abdominal disturbances of chronic arthritis might be associated with nutritional deficiency, and at the request of Dr Fletcher this investigation was undertaken in an attempt to prove or disprove the theory. Our first step was to demonstrate the incidence and type of colonic abnormalities in arthritic cases. When this had been done, we proceeded by periodical examinations, to demonstrate the effect of suitable diet upon the clinical progress, and the roentgenological appearance of the large bowel. In many cases the return to a normal appearance was indeed amazing. In others, and these were, we believe, complex cases, where nutrition alone played only a minimum part, the changes were slight or absent. It was, however, extremely interesting to note that in the majority of cases the improvement noted on the film bore a close relation to the improvement noted clinically. Latterly, we have been able with a very fair degree of accuracy, to state from the roentgenological examination, the amount of improvement, shown clinically, without any progress history being supplied from the clinician. Also, it has been possible after the first examination in some cases to give a prognosis pointing towards failure that has been borne out by the patient's subsequent course.

The roentgenological investigation may be carried out by use of the barium meal or the opaque enema. By the meal, the rate of progress or mobility will be demonstrated, and we must say we prefer the one-meal method to the two-meal one. In us-

ing the former, observations are made at the time of ingestion and at periods of six, ten, twenty-four, forty-eight, and seventy-two hours. If this is done a better understanding of the motility in each case will be obtained. The ten-hour observation is of great value. The head of the column has passed beyond the splenic flexure, the right lower quadrant is not obscured by coils of small bowel, and the appendix if filled is better seen and manipulated than at the six-hour observation.

In the vast majority of the arthritic cases examined, we saw no undue racing of the meal, the time of advance of the column's head being quite normal. In the cases showing hypermotility and spasticity, we were frequently able to demonstrate the constricted ascending colon due to a veil, and the markedly atonic cecum, but these cases indeed were few. The cecum was low in the pelvis, atonic in type, but not unduly free, demonstrating that no abnormal mesentery was present. The position of the ileocecal valve when demonstrated by an incompetency was normal, thus showing no rotation. The appendix when visualized, in very few of the cases was placed retroceally, or in an abnormal position. The ascending colon appeared well filled, often longer than usually seen, no narrowing was observed, and the haustral markings were much decreased in depth. The transverse colon showed an increase in length, often festooned in type, the haustral markings poor, or entirely absent, and the so-called "H" formation was conspicuous by its absence. The descending colon shows a definite increase in length, varying from a slight

elongation to a marked redundancy, and reduplication with lessened haustral markings

The enema gives much more evidence in our opinion than the meal, and in our re-examining of any case, the clysma is administered at intervals of about one month, comparing the various films at the completion of each examination

Might we stress here the value of the fluoroscopic screen in conjunction with the film. During the flow of the clysma under the screen, the whole bowel may be palpated. The chance of not observing any evidence of narrowing, adhesions, veils or rotation, is to a great degree eliminated. Occasionally mass peristalsis will occur after the screen examination, and when the film is made the evidence has been obscured by this. The cecum will fill well, it will be placed low in the pelvis, and marked lack of tone is noted. The transverse diameter of the cecum will be increased, and the enlargement will be noted extending to a greater or less degree up the ascending colon. No narrowing of the ascending colon will be seen that may be due to a veil, nor do we see evidence of rotation.

The hepatic flexure as a rule may be noted about the level of the first lumbar vertebra, but occasionally in the very advanced cases it will be displaced downwards. When the transverse colon fills, it will be noted the haustral markings are lessened or absent, and the transverse diameter of the bowel is increased. The total length of the transverse is also greater than usually seen, and instead of the usual "H" appearance presented by the hepatic flexure the transverse colon

and the splenic flexure, the bowel has assumed an irregular festooned position across the abdomen. The splenic flexure is held in about its usual position, but in the more advanced cases, we have noted a downward displacement there.

The descending colon shows a redundancy in many cases, frequently complete reduplication of the bowel will be noted, and tone has become less, with haustral markings poor. In the cases showing extreme change, a complete disorientation of the colon is noted.

As mentioned above, re-examination has been carried out on a large number of these cases. These examinations are spaced about one month apart. The findings at these periods were in many cases very gratifying indeed. At these observations the cecum is held at a higher level in the pelvis, the transverse diameter is lessened, and haustral markings are returning. In some of the cases this is very marked. The ascending colon shows better haustration and on measuring the longitudinal diameter of the cecum and ascending colon we have noted a decrease of as much as two inches. The transverse colon presents a lessened transverse diameter its total length is decreased and the haustral markings are improved. This shortening of the ascending and transverse colon leads one to believe the longitudinal fibres play a definite part in the changes taking place. The festooning has disappeared and a return toward the "H" type is noted.

The descending colon presents its changes also. The reduplication will be noted to have lessened in extent.

tone has improved, and haustration is better. The appearance present throughout the whole colon is that of increasing tone, returning to or at least approaching the appearance of a normal tonic colon.

In reviewing the cases examined, of which we now have about two hundred in the department, the changes mentioned above were present in 66 per cent, and improvement was present in a great majority. Coincident with the improvement of the roentgenological appearance, the clinical picture also gives a definite change for the better, reaching in some a complete amelioration of the symptoms.

All of these cases have been ob-

served under careful control. Some had been confined to bed for many months, previous to the institution of treatment. One or two were not confined to bed at any time during the investigation. At the time that dietetic treatment was undertaken all other remedial measures were discontinued, or had never been instituted.

From the foregoing observations, there seems to be no doubt that tone and motility of the large bowel are dependent on the nature of the diet, and in cases of atony definite improvement may be expected by these dietetic measures. Further, the improvement in the general condition of the patient and the amelioration of the



FIG 5



FIG 6

FIGS 5 and 6 N. B., aged 26. Rheumatoid arthritis started in 1922. Some improvement in 1924 following tonsillectomy. Later disease became more severe and from 1926 was confined to bed. Admitted May 28, 1928, showing advanced fibrous change in knees and ankles, ankylosis of hips and atrophy of muscles and bone. No further focus of infection found. The changes shown above occurred during four months of dietetic treatment. There has been slow but continued clinical improvement during the course of dietetic treatment.

symptoms coincident with the changes demonstrated by the roentgenological observation, leads us to believe that malnutrition is playing a part in the clinical picture of arthritis, and those atonic changes are a definite expression of the malnutrition.

These investigations have been carried out upon patients with rheumatoid-arthritis and osteoarthritis, and the colonic changes above described have been present in both types. The rheumatoid-arthritic group has shown the greater colonic changes and the more

improvement under dietetic treatment. We do not wish to create the impression that we consider the colonic changes described above as the primary abnormality, rather they are indicative of some other pathological process of more importance, due to nutritional deficiency, which is an important factor in the evolution of arthritis.

Dr Fletcher has followed two general principles in his dietary treatment of these cases. First the liberal ad-



FIG. 7



FIG. 8

FIGS 7 and 8. A. E., was in the hospital from Dec. 3, 1930 to Feb. 28, 1931. Five or six years ago patient began to develop pain and swelling of various joints of body with some limitation of movement. Four years ago had developed marked limitation of movement of right shoulder-joint following radical breast amputation (for scirrhous carcinoma). Arthritic involvement was in right elbow first then left wrist, right and both knees and ankles and then left shoulder. More recently within last 2 years both hands have been involved (small joints). Shortly after onset of joint pains had teeth and tonsils removed. Three weeks before admission patient first noticed swelling over sternum which was prominent (at right sterno-clavicular joint) on admission. Swelling it slightly reddened and tender. This swelling largely subsided in hospital and there was moderate improvement in other joints. Marked improvement in arthritis during residence in hospital and definite improvement in colon as shown in the films.

ministration of vitamins, especially vitamin B, secondly, a change in the balance of diet. He gives liberally food high in vitamins such as fresh vegetables and fruits, cream, butter, eggs and liver, and vitamin B is increased by administration of baker's

or brewer's yeast or wheat germ. The last appears the more effective upon these disturbances of the colon. Fifty to sixty grams of protein are given in the form of meat, fish, eggs, or liver. Fat is exhibited according to the patient's caloric requirements.

BIBLIOGRAPHY

- ¹GOLDTHWAITE, J. E., and BROWN, L. T. The cause of gastropstosis and enteroptosis with their possible importance as a causative factor in the rheumatoid diseases, *Boston Med and Surg Jr*, 1910, clxii, 695-703.
- ²LANE, SIR A. Chronic intestinal stasis. *Surg Gynec Obst*, 1910, xl, 495-500.
- ³BASSLER, A. Discussion of the surgical theories of intestinal stasis, *Jr Am Med Assoc*, 1914, lxxiii, 1469-1473.
- ⁴DANIEL, P. Septic infection versus chronic intestinal stasis, The legality of ileo-colostomy for arthritis, *Clin Jr*, 1913, xli, 305-320.
- ⁵KEITH, A. A new theory of the causation of enterostasis, *Lancet*, 1915, ii, 371-375.
- ⁶JORDAN, A. C. Radiography in intestinal stasis, *Lancet*, 1911, ii, 1824-1828. A discussion on alimentary toxemia, its sources, consequences and treatment, *Proc Roy Soc of Med*, 1913, vi, 311-315.
- ⁷SMITH, R. Relation of surgical pathology of right lower quadrant to arthritis, *Jr Bone and Joint Surg*, 1928, x, 57-61.
- ⁸TAYLOR, R. G. Surgical lesions of right lower quadrant, demonstrated in patients with chronic deforming arthritis by x-ray opaque meal examinations, *Jr Bone and Joint Surg*, 1928, x, 62-68.
- ⁹PEMBERTON, R. The metabolism and treatment of rheumatoid arthritis, *Am Jr Med Sci*, 1917, cliv, 678-692.
- ¹⁰FLETCHER, A. A. Chronic arthritis, *Canad Med Assoc Jr*, 1922, xii, 633-637.
- ¹¹MCGARRISON, R. Studies in deficiency diseases, Oxford University Press, London, 1921.

Total Occlusion of the Right Branch of the Pulmonary Artery By An Organized Thrombus*†

By J H MEANS, M D, F A C P, and T B MALLORY, M D,
Boston, Mass

THE following case, because of the apparent rarity of one of the lesions found, total thrombotic occlusion of a main branch of the pulmonary artery, and the interest of its physiological connotations, is considered worth reporting

The existing literature contains but few cases of such occlusion of a main branch, although multiple thromboses of the smaller arteries appear fairly common. A case of that sort has recently been reported by Frothingham¹. A monographic article by Posselt² in 1909 reviews thoroughly all types of pulmonary artery disease, and may be considered to cover the literature up to that time. He was able to find only three cases of complete occlusion of the pulmonary artery or one of the major branches.

The first was that of von Jurgensen. It may be summarized as follows:

The patient was a male, sixty years of age who had had dyspnea for several years which had become distinctly troublesome during the last six weeks. Physical examination showed dyspnea and marked cyano-

sis, respirations 40, pulse 88, beat irregular and distinctly intermittent. The lungs were emphysematous. The heart was enlarged to percussion, especially to the right. The sounds were all weak, but the pulmonic seemed especially weak in comparison with the aortic. There was sclerosis of the peripheral arteries. The day after entry he had a sudden slight hemiplegia with left facial paralysis and difficulty in speech. During the following two days indefinite pulmonary signs developed which were associated with a bloody sputum and it was thought he probably had pneumonia. On the third day he suddenly developed convulsions and died.

Autopsy showed the main trunk of the pulmonary artery completely occluded by a pale, reddish-gray thrombus, one inch in length, which was loosely but definitely adherent to the wall. Attached to it were several smaller, redder and fresher looking thrombotic masses. They were less adherent than the large, grayish mass. The right pulmonary artery also contained a completely occluding older thrombus, which was also adherent. The vessels in the region of the thrombi showed patches of atheroma. The heart was enlarged with hypertrophy of both ventricles. Thrombi were present between the columnar cardiac in the right ventricle. The valves showed no abnormality. The lungs showed interspersed areas of emphysema and collapse. A few small infarcts were present. An acute primary tuberculosis was found with tubercles in the lungs, liver, bronchi and retroperitoneal glands. No evidence of hypertrophy of the bronchial arteries was found.

*From the Medical Clinic and Pathological Laboratory of the Massachusetts General Hospital.

†Received for publication May 27 1931.

though von Jurgensen assumes in his discussion that the lungs must have been nourished in this way

Posselt also found two cases reported by Hart. They were in brief as follows

Case I A woman with signs and symptoms of heart disease consisting of a mitral systolic murmur, dyspnea and cyanosis, particularly of the fingertips, died under observation in the hospital with symptoms of gradually increasing decompensation

The autopsy showed marked cardiac hypertrophy of both the left and right sides of the heart. There was a well marked mitral stenosis with a fresh verrucose endocarditis. A thrombus was found in the pulmonary artery which completely occluded the main stem and the right primary branch and partially occluded the left primary branch. It showed definite lamellation and evidently had been deposited in layers. There was well marked organization at the periphery. The lungs showed extensive pleural adhesions. They were normal in volume, only slightly increased in consistency, crepitant throughout, and very rich in blood

Case II A man with symptoms of tabes dorsalis of five years' duration developed a pyelonephritis. Three weeks before death he developed what was apparently a slight bronchitis but associated with it was a marked impairment of his general condition ("Störung des Allgemeinbefindungs")

At autopsy a pale, grayish-red thrombus with indistinct lamellation was found which completely occluded the main stem and the right primary branch and partially occluded the left branch. There was no cardiac hypertrophy. The lungs were of normal volume, air-containing throughout and hyperemic. In the iliac vein an older, totally occluding thrombus was found. Microscopic examination confirmed the organization at the periphery of the lungs in both cases. In neither case was an increase in diameter of the bronchial artery demonstrated

Barnes and Yater² in 1929 reported a case of thrombosis of the large pulmonary arteries

A man of 34, was seen first in August, 1926, when he complained of dysphagia and vomiting associated with marked dyspnea on effort. Fifteen months previously he had had a septicemia following a hand infection, and four months previously a sudden attack of pain in the left chest, worse on deep breathing, and a week later similar pain on the right. Examination revealed no adequate explanation of these complaints. A positive Wassermann was found and anti-luetic treatment was given. He gradually improved and got back to work. In the autumn of 1926 there was some suggestion of lung abscess, but this did not persist

On re-examination in March and October, 1927, and March, 1928, there was found evidence of congestive heart failure, marked cardiac hypertrophy and gallop rhythm. The pulmonic second sound was greatly accentuated and the electrocardiogram showed right ventricular preponderance. He gradually became more and more dyspneic and edematous and died of progressive cardiac failure in September, 1928. In the late stages of his illness he developed an erythrocytosis

The significant autopsy findings were old thrombi in the main trunk of both pulmonary arteries and hypertrophy of the right ventricle. The thrombi were dense, white masses, about 4 cm long and 0.5 cm-1.0 cm in diameter, in the pulmonary arteries between the main trunk and the subdivision of the arteries into their branches. These thrombi greatly reduced the lumina of the arteries, the right more than the left. They were firmly adherent to the walls. The arteries were not sclerotic and appeared to be dilated. The heart valves were normal except for the mitral, which showed some verrucose, rheumatic endocarditis. The coronaries were not sclerosed but appeared dilated. Some chronic adhesive pleuritis (bilateral) and pericarditis were found, also bronchiectasis with abscess-formation in the base of the upper right lobe. Grossly the lungs showed little other evidence of disease

The authors comment on the unusual problem in diagnosing serious heart failure without obvious expla-

nation There had been no evidence of valvular, hypertensive, or coronary disease The cardiographic findings and the loud pulmonic second sound led to a diagnosis of cardiac failure, chiefly of the right heart, due to some obstruction in the pulmonary circuit The finding of the pulmonary thrombosis made it clear that the history of seizures of pain in the chest with dyspnea denoted embolism The obstruction of the pulmonary circulation by the subsequent thrombosis threw extra work on the right heart and caused failure

Jump and Baumann⁴ have also published a case of pulmonary artery thrombosis with chronic cyanosis and polycythemia

A man of 48 was admitted to the Philadelphia General Hospital complaining of swelling of the legs of two weeks' duration He had also more recently had dyspnea and palpitation on effort On examination he showed slight edema and very marked cyanosis of the face, especially dark around the nose and lips There was also moderate cyanosis of the extremities The heart was not enlarged and there was a soft systolic blow at the apex, not transmitted The liver was palpable 5 cm below the costal margin The pulse ranged from 60 to 80 and the red blood cell count varied from 5,200,000 to 7,700,000 The blood pressure was 130/80 The electrocardiogram showed right ventricular preponderance After two months in a stationary state, except for gradually increasing cyanosis he died with signs of right heart failure

The autopsy showed right ventricular hypertrophy and dilatation The pulmonary artery was dilated About two inches from the orifice was a large thrombus attached to the posterior wall and extending into both branches The left side of the heart was not remarkable the valves were normal The left lung was voluminous markedly congested and dark purplish-red in color Section of the pulmonary artery showed con-

siderable thrombotic material firmly attached to the walls and extending to the smaller subdivisions The thrombus was large enough almost to occlude the vessel Underlying it there was some arteriosclerosis The right lung was congested and also showed some tuberculosis The right branch of the pulmonary artery showed the same changes as the left, i.e., marked thrombosis and moderate arteriosclerosis The liver and spleen showed chronic passive congestion The first portion of the aorta showed moderate arteriosclerosis Jump and Baumann point out a close resemblance between the symptomatology in their case and that of so-called Auerza's disease

More recently Brenner⁵ has reported six cases in which were found thromboses of large branches (not main branches) of the pulmonary artery In all but one there was microscopic evidence of organization of the thrombi This author concludes that the thrombosis usually occurs after severe congestive failure has set in and produces no evident additional symptoms, though it probably hastens the end

Our own case is as follows

CASE REPORT

An American business man of 60 entered the private ward of the Massachusetts General Hospital as the patient of one of us (J. H. M.) on November 11, 1929 obviously in a terminal stage of congestive heart failure

No history of rheumatic disease could be obtained and it was quite certain that he had never had syphilis He had for some years been a patient of Dr. James B. Herrick of Chicago to whom we are indebted for considerable information Among other things Dr. Herrick wrote us the following

"He came to me first in 1905 for a trouble entirely unrelated to his heart

At that time I recorded in notes a very faint murmur I did not see him again for ten or twelve years but have seen him on several times since I was at the time

he was laid up with an attack of renal colic with marked hematuria. The X-ray showed stone. Both Dean Lewis and I felt in view of his heart condition and the comparative harmlessness of the stone in the kidney that an operation should not be done."

In 1922 he had an operation upon his thyroid by Dr J M T Finney of Baltimore. He had had a goiter for several years and it was apparently a familial affair occurring also in three or four of his immediate relatives. Dr Finney wrote to us as follows: "He presented himself to me in the summer of 1922 with large, toxic, multiple adenomata of the thyroid. He was suffering from pressure on the trachea, as well as from toxemia.

"Although he was not a good risk, I advised operation, which was done in June, 1922. The thyroid proper was pretty well displaced by several large adenomata, which involved pretty much the whole gland. They were partly sub-sternal and partly above, displacing the trachea quite markedly. Operation was made more difficult on account of free bleeding from the large vessels, as well as from the size of the gland, and from the fact that a large adenoma was retro-sternal and could be delivered with difficulty. Only a small portion of the glandular tissue was left, that was posterior, and was thought to be sufficient to provide function as well as to insure no injury to the parathyroids." He made a satisfactory recovery, and some dyspnea which had been present before operation disappeared. In fact he became wonderfully well.

In other respects the past and family stories seemed unimportant.

The symptoms which led up to his final illness began in September, 1928, with slight dyspnea on effort. This was relieved for a time by digitalis. In November, 1928, according to Dr Herrick, "he had an acute and very violent respiratory tract infection, resembling in every respect the influenza we had in 1918. His temperature was about 105°. He had no leucocytosis. There was definite consolidation in patches. He became extremely cyanotic and orthopneic and it looked as though he were going to die. He was pretty heavily digitalized and he pulled through."

He made some improvement after the infection, but was never really well again. In January, 1929, he got to Florida, but the trip tired him so badly that he led a bed or wheel chair existence there. He was having definite cardiac symptoms, dyspnea, and edema of ankles. In March he was moved to Atlantic City where he stayed in bed for two months on digitalis, with a slow and gradual improvement. During this time he had several nosebleeds. In May he went to his summer home in Vermont. After arriving there he stayed in bed for two weeks on digitalis and a restricted diet. By the middle of June he was much better, he could lie flat, breathe fairly well and walk slowly about the garden.

This improvement was maintained until the beginning of October, when his dyspnea and edema of his lower extremities returned, gradually increasing in degree. From October 10 on he had orthopnea and during the two weeks or so prior to entry, gradually increasing cyanosis. He had had practically no cough or sputum and no pain in the chest or palpitation. There had been some attacks of restlessness at night, but no sudden dyspnea, choking or wheezing. No headache, visual disturbance, nausea or vomiting had been present. There had been considerable heartburn. He had had nocturia, once per night, during the summer, with apparently a fairly normal total output of urine.

As he was steadily getting worse it was decided to transfer him to the Massachusetts General Hospital.

On arrival (November 11), after an one hundred and fifty mile motor ride, which he stood surprisingly well, examination showed him to be a cyanotic, orthopneic man with Cheyne-Stokes breathing and pin point pupils (morphine). The cyanosis was of medium intensity and generalized. The heart was enormous, the left border being in the mid-axillary line and there was a heaving impulse over a wide area in the sixth and seventh interspaces. No enlargement to the right was made out, nor any increase in supracardiac dullness. There was a loud, double murmur audible over the entire precordium and outward along the clavicles and, to a slight extent, up into the neck.

This double murmur was most loudly heard in the aortic area. At the apex there were three blowing murmurs giving a gallop sound. The only normal heart sound heard was a rather weak P_2 . No friction or thrills were made out. The rate was 82 and the rhythm regular. The blood pressure varied from 140 to 170 systolic over 20 diastolic. The neck veins were somewhat engorged.

The lungs were surprisingly clear. There was good resonance throughout with normal breath sounds. There were a few crackles at each base. The abdomen was slightly distended, but otherwise negative. The liver was not felt. There was moderate, soft edema of both lower legs, lower back and inner aspects of the thighs, but not of the scrotum. In all other respects the physical examination seemed unimportant. The scar of thyroidectomy was noted in the neck, but no evidence of thyroid tissue was discovered.

In hospital through November 13 his condition remained critical but without important change. Digitalization was maintained and in addition theocine was given. No diuresis was produced. The outstanding difficulties were the respiratory distress and cyanosis, and yet no physical signs of importance could be discovered in the lungs.

On November 14, after large doses of caffeine, the Cheyne-Stokes breathing gave way to an equally distressing type of regular breathing. On that day there was noted some edema of the left arm, and the temperature which had been subnormal until then, rose to 103°F . He gradually sank into a stupor, the breathing became very jerky and on the morning of November 15 he died. The pulse rate of 100 at entry rose to 120 the morning of his death.

The laboratory work obtained during this brief stay in hospital was as follows. Four examinations of the urine showed specific gravities of 1.020 to 1.030, a large trace of albumin in all specimens, sugar in none. The urines were all acid and cloudy and the sediments all showed red blood cells, white blood cells and many hyaline casts. The white blood cell count on November 12 was 19,700 and on the 14th, 17,000. The non-protein nitrogen of the blood on November 12 was 66 mg per 100 cc. The Hinton

test on the blood was negative. The electrocardiogram showed a regular rhythm rate 100, with slurred QRS in all leads, moderate left axis deviation, intraventricular block, probably right bundle branch type, also auricular-ventricular block and upright T_1 and T_2 and diphasic T .

The *clinical diagnosis* was arteriosclerotic and hypertensive heart disease with dilatation and marked hypertrophy of the heart, aortic valve disease with regurgitation, congestive failure, chronic passive congestion and terminal bronchopneumonia. The last was by inference only since no physical signs of pneumonia had been found. The nature of the aortic lesion was thought to be arteriosclerotic, since no evidence whatever of either syphilis or rheumatic infection had been obtained. This note was also made before death: "The deep cyanosis would suggest some factor in the lesser circulation but the lungs are surprisingly clear showing only a few unimportant crackles at the base." Congestive failure was regarded as the chief cause of death with bronchopneumonia a contributory cause.

The *post mortem examination* showed a remarkable variety of unusual lesions. The most striking was a complete thrombotic occlusion of the right pulmonary artery. Beginning exactly at the bifurcation the artery was completely filled by a reddish-gray somewhat friable adherent mass which extended about a centimeter into each of the three main branches of the artery within the hilus of the lung. There was no evidence either grossly or microscopically of canalization but the character of the clot and its degree of organization at the periphery suggested that it must have been pass-

he was laid up with an attack of renal colic with marked hematuria. The X-ray showed stone. Both Dean Lewis and I felt in view of his heart condition and the comparative harmlessness of the stone in the kidney that an operation should not be done."

In 1922 he had an operation upon his thyroid by Dr J. M. T. Finney of Baltimore. He had had a goiter for several years and it was apparently a familial affair occurring also in three or four of his immediate relatives. Dr Finney wrote to us as follows: "He presented himself to me in the summer of 1922 with large, toxic, multiple adenomata of the thyroid. He was suffering from pressure on the trachea, as well as from toxemia.

"Although he was not a good risk, I advised operation, which was done in June, 1922. The thyroid proper was pretty well displaced by several large adenomata, which involved pretty much the whole gland. They were partly sub-sternal and partly above, displacing the trachea quite markedly. Operation was made more difficult on account of free bleeding from the large vessels, as well as from the size of the gland, and from the fact that a large adenoma was retro-sternal and could be delivered with difficulty. Only a small portion of the glandular tissue was left, that was posterior, and was thought to be sufficient to provide function as well as to insure no injury to the parathyroids." He made a satisfactory recovery, and some dyspnea which had been present before operation disappeared. In fact he became wonderfully well.

In other respects the past and family stories seemed unimportant.

The symptoms which led up to his final illness began in September, 1928, with slight dyspnea on effort. This was relieved for a time by digitalis. In November, 1928, according to Dr Herrick, "he had an acute and very violent respiratory tract infection resembling in every respect the influenza we had in 1918. His temperature was about 105°. He had no leucocytosis. There was definite consolidation in patches. He became extremely cyanotic and orthopneic and it looked as though he were going to die. He was pretty heavily digitalized and he pulled through."

He made some improvement after the infection, but was never really well again. In January, 1929, he got to Florida, but the trip tired him so badly that he led a bed or wheel chair existence there. He was having definite cardiac symptoms, dyspnea, and edema of ankles. In March he was moved to Atlantic City where he stayed in bed for two months on digitalis, with a slow and gradual improvement. During this time he had several nosebleeds. In May he went to his summer home in Vermont. After arriving there he stayed in bed for two weeks on digitalis and a restricted diet. By the middle of June he was much better, he could lie flat, breathe fairly well and walk slowly about the garden.

This improvement was maintained until the beginning of October, when his dyspnea and edema of his lower extremities returned, gradually increasing in degree. From October 10 on he had orthopnea and during the two weeks or so prior to entry, gradually increasing cyanosis. He had had practically no cough or sputum and no pain in the chest or palpitation. There had been some attacks of restlessness at night, but no sudden dyspnea, choking or wheezing. No headache, visual disturbance, nausea or vomiting had been present. There had been considerable heartburn. He had had nocturia, once per night, during the summer, with apparently a fairly normal total output of urine.

As he was steadily getting worse it was decided to transfer him to the Massachusetts General Hospital.

On arrival (November 11), after an one hundred and fifty mile motor ride, which he stood surprisingly well, examination showed him to be a cyanotic, orthopneic man with Cheyne-Stokes breathing and pin point pupils (morphine). The cyanosis was of medium intensity and generalized. The heart was enormous, the left border being in the mid-axillary line and there was a heaving impulse over a wide area in the sixth and seventh interspaces. No enlargement to the right was made out, nor any increase in supracardiac dullness. There was a loud double murmur audible over the entire precordium and outward along the clavicles and, to a slight extent, up into the neck.

This double murmur was most loudly heard in the aortic area. At the apex there were three blowing murmurs giving a gallop sound. The only normal heart sound heard was a rather weak P_2 . No friction or thrills were made out. The rate was 82 and the rhythm regular. The blood pressure varied from 140 to 170 systolic over 20 diastolic. The neck veins were somewhat engorged.

The lungs were surprisingly clear. There was good resonance throughout with normal breath sounds. There were a few crackles at each base. The abdomen was slightly distended, but otherwise negative. The liver was not felt. There was moderate, soft edema of both lower legs, lower back and inner aspects of the thighs, but not of the scrotum. In all other respects the physical examination seemed unimportant. The scar of thyroidectomy was noted in the neck, but no evidence of thyroid tissue was discovered.

In hospital through November 13 his condition remained critical but without important change. Digitalization was maintained and in addition theocine was given. No diuresis was produced. The outstanding difficulties were the respiratory distress and cyanosis, and yet no physical signs of importance could be discovered in the lungs.

On November 14, after large doses of caffeine, the Cheyne-Stokes breathing gave way to an equally distressing type of regular breathing. On that day there was noted some edema of the left arm, and the temperature which had been subnormal until then, rose to 103°F . He gradually sank into a stupor, the breathing became very jerky and on the morning of November 15 he died. The pulse rate of 100 at entry rose to 120 the morning of his death.

The laboratory work obtained during this brief stay in hospital was as follows. Four examinations of the urine showed specific gravities of 1.020 to 1.030, a large trace of albumin in all specimens, sugar in none. The urines were all acid and cloudy and the sediments all showed red blood cells, white blood cells, and many hyaline casts. The white blood cell count on November 12 was 19,700 and on the 14th, 17,000. The non-protein nitrogen of the blood on November 12 was 66 mg per 100 cc. The Hinton

test on the blood was negative. The electrocardiogram showed a regular rhythm, rate 100, with slurred QRS in all leads, moderate left axis deviation, intraventricular block, probably right bundle branch type, also auricular-ventricular block and upright T_1 and T_2 and diphasic T_3 .

The *clinical diagnosis* was arteriosclerotic and hypertensive heart disease with dilatation and marked hypertrophy of the heart, aortic valve disease with regurgitation, congestive failure, chronic passive congestion, and terminal bronchopneumonia. The last was by inference only since no physical signs of pneumonia had been found. The nature of the aortic lesion was thought to be arteriosclerotic, since no evidence whatever of either syphilis or rheumatic infection had been obtained. This note was also made before death, "The deep cyanosis would suggest some factor in the lesser circulation but the lungs are surprisingly clear, showing only a few unimportant crackles at the base." Congestive failure was regarded as the chief cause of death with bronchopneumonia a contributory cause.

The *post mortem examination* showed a remarkable variety of unusual lesions. The most striking was a complete thrombotic occlusion of the right pulmonary artery. Beginning exactly at the bifurcation the artery was completely filled by a reddish-gray, somewhat friable, adherent mass which extended about a centimeter into each of the three main branches of the artery within the hilus of the lung. There was no evidence either grossly or microscopically of canalization, but the character of the clot and its degree of organization at the periphery suggested that it must have been pres-

ent weeks or possibly months. The right lung, however, showed no trace of necrosis or of scarring. It contained much less blood than the left lung, which presented the usual picture of chronic passive congestion. It was smaller and slightly less crepitant than the left, yet it contained air throughout all portions and showed no evidence of collapse.

The absence of necrosis could of

course be explained only by the development of a compensatory circulation. Evidence of this was readily found. Three arteries of unusual size led into the hilus region. The first was evidently a greatly hypertrophied bronchial artery, estimated to be four times the diameter of the normal bronchial artery. Two other vessels of unusual size compared with control specimens, ran along the sides of the



FIG. 1. Anterior view of the lungs one-third the original size. The right pulmonary artery has been opened to show a completely occluding thrombus, which on microscopic examination showed early organization at its periphery. The right lung is slightly smaller than the left but shows no infarction.

trachea anastomosing at their lower ends with the hypertrophied bronchial artery, and passing into the right hilus. They were traced upwards into the neck where they probably arose from the inferior thyroid arteries which supply the trachea, though the dissection was not carried high enough to demonstrate their origin.

Further examination of the right lung revealed several other findings of interest. In the region of the hilus was an irregular, pyramidal, calcified and partially ossified mass approximately 3 by 3 by 2 cm. It completely surrounded the primary bronchial branches which passed unobstructed through the area, though their walls were calcified. It also surrounded the first branches of the pulmonary artery which passed through the area without narrowing of their lumina. They were, however, occluded by thrombi continuous with the large thrombus in the main artery, but in this region the clot was redder, softer, less adherent and apparently of more recent origin. Microscopic examination of this region showed a mass of almost acellular, hyalinized and partially calcified, fibrous tissue in which were numerous foci of ossification containing well differentiated bone trabeculae separated by fatty and, in places, hematopoietic marrow. No foci of caseation and no areas suggestive of tuberculosis could be identified.

The pulmonary arteries beyond the point of thrombosis were entirely normal in appearance until the peripheral portion of the lung was reached, where many were found partially or completely occluded by fibrous plugs typical in appearance of completely organ-

ized thrombi. Many of these showed canalization. It is particularly interesting that exactly similar lesions were found in corresponding peripheral portions of the left lung.

The capillaries of the alveolar walls were difficult to make out, and very few red blood cells were found in the septa. The lumina of the alveoli, which in the congested left lung contained hemosiderin-filled "heart lesion cells", serum and occasional red blood cells, were for the most part empty or contained a mucoid secretion. The epithelium of many of the alveolar sacs showed a metaplasia into a high cuboidal or even low columnar type.

The other finding of greatest importance was in the heart. It was greatly hypertrophied, weighing 995 gm. The hypertrophy was shared between the two ventricles, both of which were greatly dilated, their walls hypertrophied. The right ventricle was proportionately slightly more hypertrophied, its walls measuring 7 mm in thickness, whereas the left measured 16 mm. Both auricles showed moderate dilatation. The aortic valve was bicuspid—evidently a congenital lesion. It also showed marked calcification of both its cusps so that they were practically immobile and fixed in a position to cause both stenosis and regurgitation. The other valves were negative and the coronaries showed only occasional patches of atheroma without narrowing of the lumina.

A substernal colloid goiter weighing 75 gm and a smaller separate one weighing 5 gm were found in the anterior mediastinum above and anterior to the great vessels. It was not felt that they played a part in the symp-



FIG. 2 The hilus of the lung viewed from behind with the trachea and primary bronchi laid open. The aorta has been dissected free and reflected laterally to show the greatly hypertrophied bronchial artery passing behind the hilus glands.

tomatology An incidental finding was a calculus in the right renal pelvis with an adjacent papilloma of the epithelium

DISCUSSION

The variety of unusual lesions found in this patient makes attempts at interpretation of their interrelations both interesting and baffling. Congenital bicuspid valves are ordinarily competent and the stenosis and regurgitation, evidence of which was noted first at the age of thirty-six, must be considered an acquired lesion. Syphilis was readily ruled out by the serologic studies in life and by the autopsy findings. The process might have been either rheumatic or arteriosclerotic in origin, the latter seeming to us more consistent with the anatomic findings, with the absence of mitral involvement, the late onset, and the lack of history of rheumatic fever.

The renal stone was evidently a side issue and the goiter, past history with no probable bearing upon the present illness.

The complete plugging of the pulmonary artery without necrosis, with the probable duration of life of weeks to months since its occurrence struck us as quite remarkable. Two possibilities came up for consideration, the local formation of the thrombus, or an embolus from some undetermined source. Local thrombus formation almost always presupposes local vascular injury. It was not thought that the calcified mass in the hilus of the lung could have been responsible, for although it completely surrounded the chief branches of the artery, it did not narrow them and their inner surfaces were in no way involved. On the

other hand it seemed fair to assume that an embolus could not have been totally occluding from the start since so sudden a strain upon an already damaged heart would almost certainly have been immediately fatal, or would have produced clinical symptoms of which we have no suggestion in the history. A medium sized embolus might well have lodged in the right pulmonary artery producing at first only a partial occlusion, but gradually growing by accretion into a mass which completely filled the artery. This would have allowed time for the development of the rich compensatory circulation supplied by the hypertrophied bronchial artery and the anastomosing tracheal branches. The numerous partially or completely obliterated branches of the pulmonary artery found in the peripheral portions of both lungs might be the result of a shower of minor emboli which had been completely organized and partially canalized.

The case is interesting from the point of view of morbid physiology in that it proves that an entire lung may be separated from its pulmonary artery supply and suffer no injury of any sort provided the occlusion is gradual, allowing time for the establishment of a collateral circulation from the aorta. The situation reminds one of those cases of chronic total occlusion of both coronaries without history of the characteristic picture of coronary occlusion. The effect of slow closure of the pulmonary artery is evidently different from sudden shutting off, as from embolism or ligation, in which cases the picture of infarction is produced. Sauerbruch

and Bruns⁶ experimentally found that even a main branch could be tied without disastrous consequences, but that fibrosis and shrinkage of the lung developed forthwith. They also have shown that in man in cases of bronchiectasis and tumors there is produced a marked shrinkage of the lung. Lihenthal⁷ describes one ligation of the left main branch within the pericardium for abscess. The patient survived the ligation but soon afterwards drowned in pus from the abscess.

With regard to the collateral bronchial arterial circulation the work of Holman and Mathes⁸ is of interest. These investigators found marked dilatation of the bronchial artery supplying a lobe containing an experimentally produced abscess.

From the clinical point of view it is of interest that such a gross disturbance in lung circulation can exist without altered physical signs in the lung. Since there was neither collapse nor edema, there was nothing to alter the percussion note or change the fremitus or breath sounds.

The thrombosis undoubtedly explains the cyanosis, for which no adequate explanation had been found during life, but which was thought to point to a lesion in the pulmonary circuit. Deep cyanosis is characteristic of other pulmonary artery diseases, so-

called Ayerza's disease, for example, and is probably to be explained on the basis of diminished aerating surface to which blood can be exposed with consequent greater reduction of hemoglobin in passage through the lungs.

To what extent the thrombus contributed to the heart failure is impossible to say. The patient was entitled to die of congestive heart failure without it. Our guess, however, is that it probably importantly accelerated the failure. The hypertrophy of the right ventricle would substantiate this view. The thrombus could do this both by increasing the anoxemia, as well as by producing pulmonary hypertension by diminishing the total diameter of the pulmonary arterial tree. This seems to have happened in the patient of Barnes and Yater and also in that of Jump and Baumann.

CONCLUSIONS

Total thrombotic occlusion of a main branch of the pulmonary artery may occur without damage to the lung provided it develops slowly enough to allow for the development of collateral circulation through the bronchial system.

Such a lesion may produce no local signs in the lungs but the presence of cyanosis and right-sided heart failure without other obvious cause may suggest its presence.

BIBLIOGRAPHY

- ¹FORTHINGHAM, C. A case of extensive bilateral progressive thrombosis of the smaller branches of the pulmonary arteries. *Am. Jr. Path.*, 1927, 1, 11-22.
- ²POSSLET, A. Die Erkrankungen der Lungen. *Schlagader, Ergeb. d. allg. Path. u. path. Anat.* 1909, xiii, 298-326.

BARNES, A. R., and YATER, W. M. Paroxysmal tachycardia and alternating incomplete right and left bundle-branch block with fibrosis of myocardium, failure of right ventricle due to ancient thrombus in pulmonary arteries, fibromyxoma of left auricle occluding mitral

orifice and simulating mitral stenosis, Med Clin North Am, 1929, xii, 1603-1615

¹JUMP, H D, and BAUMANN, F Large thrombus of pulmonary artery with chronic cyanosis and polycythemia, Penn Med Jr, 1929, xxvii, 754-756

²BRUNER O Sclerosis of the pulmonary artery with thrombosis, Lancet, 1931 ccvi, 911-914

³SAUERBRUCH, F Chirurgie der Brustorgane, 1920, i Julius Springer, Berlin, p 572

⁴LILIENTHAL, H Thoracic surgery, 1925, W B Saunders, Philadelphia, p 485

⁵HOLMAN, E, and MATHES, M E Production of intrapulmonary suppuration by secondary infection of sterile embolic area, experimental study, Arch Surg, 1929, xix, 1246-1261

The Therapeutic Use of Oxygen in Heart Disease*

By ALVAN L. BARACH, M D, New York City

INTRODUCTION

OXYGEN is the fundamental requirement for the transformation of energy in the body. A normal supply of oxygen to the tissues in an individual living at sea level atmospheric pressure is maintained essentially by intact respiratory and cardiac systems. Although the metabolism is not altered by an increase in the oxygen supply (Voit,¹ Pfluger,² and Benedict and Higgins,³) reduction in the normal amount of oxygen furnished to the tissues results in profound alterations in the chemical processes of the body. A state of oxygen-want or anoxemia may be produced by a diminished concentration of oxygen in the outside air or through an impairment of the respiratory or cardiac systems.

HISTORY

The direct effects of oxygen-want have been observed by many physiologists, either through studies at high altitude or through experiments in chambers in which the partial pressure of oxygen is lowered. Headache, nausea, and vomiting, irrational states and mental depression are common symptoms. The pulse is invariably elevated. The respiration is frequently periodic in char-

acter, changing to rapid and shallow breathing. In abrupt and severe want of oxygen, delirium, coma and cardiac failure occur (Haldane,⁴ Bancroft⁵).

Von Terray⁶ found, as a result of the production of severe anoxemia, an increase in the excretion of carbon dioxide, increased elimination of nitrogen and a marked production of organic acids. Schneider, Truesdell and Clarke⁷ also observed an increased elimination of carbon dioxide in periods of anoxemia which was immediately reduced by the inhalation of oxygen. Krogh⁸ reported a decrease in the rate of oxidation when the oxygen supply to the tissues was diminished beyond a certain point, namely, when the oxygen pressure in the inspired air fell below 83 mm, or atmospheric pressure of 410 mm.

The rôle of oxygen-want in the production of the symptoms of heart disease has not been clearly understood. Previous studies bearing on this factor will now be referred to. Means and Newburgh⁹ found a diminished oxygen saturation of the venous blood in cases of cardiac decompensation. These results were confirmed and amplified by Lundsgaard.¹⁰ Harrop¹¹ showed that a diminished arterial oxygen saturation was present in cases of cardiac insufficiency. Barach and Woodwell¹² administered 40 to 60 per cent oxygen over short periods of time and observed that an increase in both the arterial and venous oxygen saturations occurred. When the arterial anoxemia was due to passive congestion and edema of the bases of the lungs, oxygen treatment regularly raised the arterial saturation to the normal level. The elevation of the venous saturation seemed largely dependent upon the increase of the arterial oxygen saturation. Diminution of

*Presented at the Baltimore Meeting of the American College of Physicians, March 23, 1931. From the Department of Medicine, College of Physicians and Surgeons, Columbia University and the Presbyterian Hospital, New York City.

cyanosis and slowing of the pulse were the outstanding objective changes. There was in some cases an increase in carbon dioxide content of the arterial and venous blood. In two cases of right bundle branch block, a decreased notching and a diminished height of the R wave were present during the inhalation of oxygen.

Beddard and Pembrey¹³ found the carbon dioxide of the alveolar air reduced in cases of cardiac decompensation. This was confirmed by Fitzgerald¹⁴ and later by Porges, Leimdorfer and Markovici¹⁵ who observed that the alveolar carbon dioxide was low in cases of cardiac disease in whom dyspnea was present and normal in those without dyspnea. Peabody¹⁶ observed, in some cases of cardiac disease, that a lowered tension of the alveolar carbon dioxide was present during the dyspneic period followed by a rise when compensation was regained.

The relation between the alveolar and arterial carbon dioxide tensions was studied by Peters and Barr¹⁷ who found that the alveolar values were decidedly lower than the arterial in advanced decompensation. The same observation was noted by Campbell and Poulton¹⁸.

The carbon dioxide dissociation curves of the blood were found by Peters and Barr¹⁷ to be at normal levels in mild or moderate cardiac insufficiency but definitely reduced in certain cases of advanced heart failure, particularly those with marked cyanosis.

The H-ion concentration of the arterial blood in cardiac disease may be altered by associated pulmonary or renal disease, administration of morphine and other complicating factors. In general it has been reported to be within normal limits in mild or moderate degrees of heart failure and definitely acid in extreme failure, with return to normal when compensation was restored (Peters and Barr¹⁷). Instances of an alkaline pH in a few cases of cardiac dyspnea have been reported by Campbell and Poulton¹⁹.

In 1908 Beddard and Pembrey²⁰ observed that the inhalation of oxygen resulted in a decreased pulmonary ventilation in a patient with cardiac insufficiency. This finding was later reported by Campbell, Hunt and Poul-

ton²¹ who observed also a corresponding increase in the carbon dioxide concentration of the expired air. It is interesting to note that in normal animals living in high oxygen atmospheres, J. A. Campbell²² noted an increase in tissue tensions of both oxygen and carbon dioxide.

Recently, Baker²³ reported a case of bundle branch block in which inhalation of oxygen resulted in a disappearance of the aberrant ventricular complexes and a striking improvement in intraventricular conductivity.

RESULTS

In this communication we wish to present the results of studies of the effects of oxygen therapy in various types of heart disease done in collaboration with D. W. Richards²⁴ and R. L. Levy²⁵ at the Presbyterian Hospital, New York, during the past three years. Since one of the handicaps in the previous studies of the therapeutic use of oxygen has been that it was generally administered ineffectively, we shall note briefly the methods of oxygen therapy which we employed. The Barach oxygen chamber²⁶ and oxygen tent²⁷ were employed to administer 40 to 50 per cent oxygen. In the oxygen chamber a constant temperature and humidity regulation was achieved and in the oxygen tent the temperature was kept below 70 degrees and the humidity below 50 per cent. In the treatment of patients with dyspnea it is of the greatest importance, not only to be accurate in the determination of the oxygen concentration employed but also to provide a comfortable atmospheric environment. Oxygen therapy will not be successful if types of apparatus are used which do not effectively remove the heat and moisture eliminated by the patient, in addition to furnishing 40 to 50 per

The Therapeutic Use of Oxygen in Heart Disease*

By ALVAN L. BARACH, M.D., New York City

INTRODUCTION

OXYGEN is the fundamental requirement for the transformation of energy in the body. A normal supply of oxygen to the tissues in an individual living at sea level atmospheric pressure is maintained essentially by intact respiratory and cardiac systems. Although the metabolism is not altered by an increase in the oxygen supply (Voit,¹ Pfluger,² and Benedict and Higgins,³) reduction in the normal amount of oxygen furnished to the tissues results in profound alterations in the chemical processes of the body. A state of oxygen-want or anoxemia may be produced by a diminished concentration of oxygen in the outside air or through an impairment of the respiratory or cardiac systems.

HISTORY

The direct effects of oxygen-want have been observed by many physiologists, either through studies at high altitude or through experiments in chambers in which the partial pressure of oxygen is lowered. Headache, nausea, and vomiting, irrational states and mental depression are common symptoms. The pulse is invariably elevated. The respiration is frequently periodic in char-

acter, changing to rapid and shallow breathing. In abrupt and severe want of oxygen, delirium, coma and cardiac failure occur (Haldane,⁴ Bancroft⁵).

Von Terray⁶ found, as a result of the production of severe anoxemia, an increase in the excretion of carbon dioxide, increased elimination of nitrogen and a marked production of organic acids. Schneider, Truesdell and Clarke⁷ also observed an increased elimination of carbon dioxide in periods of anoxemia which was immediately reduced by the inhalation of oxygen. Krogh⁸ reported a decrease in the rate of oxidation when the oxygen supply to the tissues was diminished beyond a certain point, namely, when the oxygen pressure in the inspired air fell below 83 mm, or atmospheric pressure of 410 mm.

The rôle of oxygen-want in the production of the symptoms of heart disease has not been clearly understood. Previous studies bearing on this factor will now be referred to. Means and Newburgh⁹ found a diminished oxygen saturation of the venous blood in cases of cardiac decompensation. These results were confirmed and amplified by Lundsgaard.¹⁰ Harrop¹¹ showed that a diminished arterial oxygen saturation was present in cases of cardiac insufficiency. Barach and Woodwell¹² administered 40 to 60 per cent oxygen over short periods of time and observed that an increase in both the arterial and venous oxygen saturations occurred. When the arterial anoxemia was due to passive congestion and edema of the bases of the lungs, oxygen treatment regularly raised the arterial saturation to the normal level. The elevation of the venous saturation was largely dependent upon the increase of the arterial oxygen saturation. Duration of

*Presented at the Baltimore Meeting of the American College of Physicians, March 23, 1931. From the Department of Medicine, College of Physicians and Surgeons, University of Pennsylvania and the Presbyterian Hospital, Philadelphia.

cyanosis and slowing of the pulse were the outstanding objective changes. There was in some cases an increase in carbon dioxide content of the arterial and venous blood. In two cases of right bundle branch block, a decreased notching and a diminished height of the R wave were present during the inhalation of oxygen.

Beddard and Pembrey¹³ found the carbon dioxide of the alveolar air reduced in cases of cardiac decompensation. This was confirmed by Fitzgerald¹⁴ and later by Porges, Leimdorfer and Markovici¹⁵ who observed that the alveolar carbon dioxide was low in cases of cardiac disease in whom dyspnea was present and normal in those without dyspnea. Peabody¹⁶ observed, in some cases of cardiac disease, that a lowered tension of the alveolar carbon dioxide was present during the dyspneic period followed by a rise when compensation was regained.

The relation between the alveolar and arterial carbon dioxide tensions was studied by Peters and Barr¹⁷ who found that the alveolar values were decidedly lower than the arterial in advanced decompensation. The same observation was noted by Campbell and Poulton¹⁸.

The carbon dioxide dissociation curves of the blood were found by Peters and Barr¹⁷ to be at normal levels in mild or moderate cardiac insufficiency but definitely reduced in certain cases of advanced heart failure, particularly those with marked cyanosis.

The H-ion concentration of the arterial blood in cardiac disease may be altered by associated pulmonary or renal disease, administration of morphine and other complicating factors. In general it has been reported to be within normal limits in mild or moderate degrees of heart failure and definitely acid in extreme failure, with return to normal when compensation was restored (Peters and Barr¹⁷). Instances of an alkaline pH in a few cases of cardiac dyspnea have been reported by Campbell and Poulton¹⁹.

In 1908 Beddard and Pembrey²⁰ observed that the inhalation of oxygen resulted in a decreased pulmonary ventilation in a patient with cardiac insufficiency. This finding was later reported by Campbell, Hunt and Poul-

ton²¹ who observed also a corresponding increase in the carbon dioxide concentration of the expired air. It is interesting to note that in normal animals living in high oxygen atmospheres, J. A. Campbell²² noted an increase in tissue tensions of both oxygen and carbon dioxide.

Recently, Baker²³ reported a case of bundle branch block in which inhalation of oxygen resulted in a disappearance of the aberrant ventricular complexes and a striking improvement in intraventricular conductivity.

RESULTS

In this communication we wish to present the results of studies of the effects of oxygen therapy in various types of heart disease done in collaboration with D. W. Richards²⁴ and R. L. Levy²⁵ at the Presbyterian Hospital, New York, during the past three years. Since one of the handicaps in the previous studies of the therapeutic use of oxygen has been that it was generally administered ineffectively, we shall note briefly the methods of oxygen therapy which we employed. The Barach oxygen chamber²⁶ and oxygen tent²⁷ were employed to administer 40 to 50 per cent oxygen. In the oxygen chamber a constant temperature and humidity regulation was achieved and in the oxygen tent the temperature was kept below 70 degrees and the humidity below 50 per cent. In the treatment of patients with dyspnea it is of the greatest importance, not only to be accurate in the determination of the oxygen concentration employed but also to provide a comfortable atmospheric environment. Oxygen therapy will not be successful if types of apparatus are used which do not effectively remove the heat and moisture eliminated by the patient, in addition to furnishing 40 to 50 per

cent oxygen in the inspired air. In some cases when lower oxygen concentrations were employed, the nasal catheter was used to furnish 30 to 35 per cent oxygen as described in a previous article.⁴

We wish to report upon the therapeutic use of oxygen in twenty patients who may be classified under the following four headings:

- 1 Congestive heart failure due to primary cardiac disease
- 2 Cardiac insufficiency developing as a sequel to chronic pulmonary disease
- 3 Acute coronary thrombosis
- 4 Coronary arteriosclerosis with chronic cardiac pain

1 CONGESTIVE HEART FAILURE DUE TO PRIMARY CARDIAC DISEASE*

The effects of living for two to five weeks in an atmosphere containing 45 per cent oxygen were studied in eight patients with congestive heart failure by Dr. Richards and myself. Although there was a considerable variation in their pathology, from a clinical standpoint they were all cases of advanced cardiac insufficiency. All were exsanguine, suffered from dyspnea at rest and all except one had marked orthopnea and generalized edema. The patients were first observed from one to eight weeks on the ward on routine treatment. When there appeared to be no further clinical improvement or when the patient was definitely losing weight, transfer was made to the

oxygen room where the patient inspired 45 per cent oxygen.

In four patients who suffered from degenerative heart disease characterized by intense dyspnea and orthopnea, marked cyanosis and peripheral edema, the major effects of residence in an atmosphere of 45 per cent oxygen were:

(1) Marked subjective improvement, decrease of cyanosis, relief of dyspnea, orthopnea and cough, beginning generally within three hours after their entrance into a high oxygen atmosphere.

(2) Increase of urinary output and disappearance of edema, of gradual onset and usually not reaching its maximum for three to five days. In three patients a return to normal atmospheric oxygen resulted in a decreased urinary output and a return of edema. Raising the oxygen concentration again brought about a second diuresis. In two, this sequence was obtained both by transferring the patient from the oxygen room to the ward and by lowering and raising the oxygen within the chamber without removing the patient.

(3) Increased arterial oxygen saturation.

(4) Sharp rise in carbon dioxide content of arterial blood, and in carbon dioxide curve level, in high oxygen.

(5) Decreased pulmonary ventilation.

(6) Lowered pulse rate.

(7) In the case of one patient other measurements showed: (a) slight increase in cardiac output, (b) sharp fall in blood lactic acid from 220 mg. to a normal value of 7 mg.

* This study was reported by Barach, A. L., Richards, D. W., and Jones, C. R. *Proc. Soc. Exper. Biol. Med.* 45: 1-5, 1941. In *Ann. N. Y. Acad. Sci.* 45: 1-10, 1945.

In these cases, all of whom may be said to have improved in 45 per cent oxygen, there were other changes which occurred, although not constantly lowered respiratory rate, lowered body temperature, decreased basal metabolism, slightly higher arterial pH, increase in vital capacity and fall in red blood count and hemoglobin.

Two other cases had advanced and active rheumatic heart disease, with cyanosis, generalized passive congestion, edema, and irregular fever. Subjectively, they were more comfortable and less dyspneic in high oxygen, their cyanosis was somewhat improved and comparative measurements on one case showed an increase in arterial oxygen saturation from 84 to 93 per cent. There was in each case a moderate rise in carbon dioxide curve level. Little change, however, occurred in the edema, and there was no tendency to diuresis. However, one patient was removed rather abruptly from 45 per cent oxygen to the ward, where she rapidly went into collapse, with renal suppression for 20 hours, low blood pressure, and profound cyanosis. Her arterial oxygen saturation again went down to 84 per cent (this measurement was taken when patient was receiving four liters of oxygen per minute by nasal catheter), carbon dioxide dropped to the remarkably low value of 26.4 volumes per cent, and arterial pH fell from 7.44 to 7.36. After return to 45 per cent in the chamber she recovered quickly to her former state. During the next 24 hours she passed 1000 cc of urine. These two patients both showed lowered pulse rate while in high oxygen.

Finally, two patients showed practically no reaction whatever to the increase in atmospheric oxygen. One was a man of 54, with long-standing mitral stenosis, great cardiac enlargement, enlargement of the liver, but no edema and no orthopnea. Clinically, he was moderately cyanotic, but this was evidently of venous origin as his arterial blood when he was in the ward was 91 per cent saturated with oxygen or better. The development of a mild rhinitis and bronchitis with a transient lowering of the carbon dioxide curve, and of the vital capacity, seemed to be the only change while he was in the oxygen room. Subjectively, he was no better.

The second was a girl of 13 with congenital heart disease, later shown by autopsy to be the tetralogy of Fallot, combined with a patent ductus arteriosus. The case is being reported by Dr. Richards²⁹ in further detail elsewhere. It is sufficient to note here that her arterial oxygen saturation, about 60 per cent, was increased only slightly, to 65 per cent, in high oxygen, that there was no change in her carbon dioxide or in her urinary output, that her pulmonary blood flow was practically unaltered, and that subjectively she was not improved. She did not have any edema at any time. She was not in the oxygen room long enough to rule out the possibility of a change in urinary output relative to intake.

II CARDIAC INSUFFICIENCY DEVELOPING AS A SEQUEL TO CHRONIC PULMONARY DISEASE

The effects of oxygen therapy were studied in five cases of cardiac insufficiency due to previous chronic

cent oxygen in the inspired air. In some cases when lower oxygen concentrations were employed, the nasal catheter was used to furnish 30 to 35 per cent oxygen as described in a previous article²⁸

We wish to report upon the therapeutic use of oxygen in twenty patients who may be classified under the following four headings

- 1 Congestive heart failure due to primary cardiac disease
- 2 Cardiac insufficiency developing as a sequel to chronic pulmonary disease
- 3 Acute coronary thrombosis
- 4 Coronary arteriosclerosis with chronic cardiac pain

1 CONGESTIVE HEART FAILURE DUE TO PRIMARY CARDIAC DISEASE*

The effects of living for two to five weeks in an atmosphere containing 45 per cent oxygen were studied in eight patients with congestive heart failure by Dr Richards and myself. Although there was a considerable variation in their pathology, from a clinical standpoint they were all cases of advanced cardiac insufficiency. All were cyanotic, suffered from dyspnea at rest and all except one had marked orthopnea and generalized edema. The patients were first observed from one to eight weeks on the ward on routine treatment. When there appeared to be no further clinical improvement or when the patient was definitely losing ground, transfer was made to the

oxygen room where the patient inspired 45 per cent oxygen.

In four patients who suffered from degenerative heart disease characterized by intense dyspnea and orthopnea, marked cyanosis and peripheral edema, the major effects of residence in an atmosphere of 45 per cent oxygen were

(1) Marked subjective improvement, decrease of cyanosis, relief of dyspnea, orthopnea and cough, beginning generally within three hours after their entrance into a high oxygen atmosphere

(2) Increase of urinary output and disappearance of edema, of gradual onset and usually not reaching its maximum for three to five days. In three patients a return to normal atmospheric oxygen resulted in a decreased urinary output and a return of edema. Raising the oxygen concentration again brought about a second diuresis. In two, this sequence was obtained both by transferring the patient from the oxygen room to the ward, and by lowering and raising the oxygen within the chamber without removing the patient.

(3) Increased arterial oxygen saturation

(4) Sharp rise in carbon dioxide content of arterial blood, and in carbon dioxide curve level, in high oxygen

(5) Decreased pulmonary ventilation

(6) Lowered pulse rate

(7) In the case of one patient other measurements showed (a) slight increase in cardiac output, (b) sharp fall in blood lactic acid from 22.6 mg to a normal value of 7 mg

*Complete data in paper by Barach, A. L., and Richards, D. W., Effects of treatment with oxygen in cardiac failure, *Arch Int Med* 1931, XLVIII, 325.

In these cases all of whom may be said to have improved in 45 per cent oxygen, there were other changes which occurred, although not constantly lowered respiratory rate, lowered body temperature, decreased basal metabolism, slightly higher arterial pH, increase in vital capacity and fall in red blood count and hemoglobin.

Two other cases had advanced and active rheumatic heart disease, with cyanosis, generalized passive congestion, edema, and irregular fever. Subjectively, they were more comfortable and less dyspneic in high oxygen, their cyanosis was somewhat improved and comparative measurements on one case showed an increase in arterial oxygen saturation from 84 to 93 per cent. There was in each case a moderate rise in carbon dioxide curve level. Little change, however, occurred in the edema, and there was no tendency to diuresis. However, one patient was removed rather abruptly from 45 per cent oxygen to the ward where she rapidly went into collapse, with renal suppression for 20 hours, low blood pressure, and profound cyanosis. Her arterial oxygen saturation again went down to 84 per cent (this measurement was taken when patient was receiving four liters of oxygen per minute by nasal catheter), carbon dioxide dropped to the remarkably low value of 26.4 volumes per cent, and arterial pH fell from 7.44 to 7.36. After return to 45 per cent in the chamber, she recovered quickly to her former state. During the next 24 hours she passed 1000 c.c. of urine. These two patients both showed lowered pulse rate while in high oxygen.

Finally, two patients showed practically no reaction whatever to the increase in atmospheric oxygen. One was a man of 54, with long-standing mitral stenosis, great cardiac enlargement, enlargement of the liver, but no edema and no orthopnea. Clinically, he was moderately cyanotic, but this was evidently of venous origin as his arterial blood when he was in the ward was 91 per cent saturated with oxygen or better. The development of a mild rhinitis and bronchitis with a transient lowering of the carbon dioxide curve, and of the vital capacity, seemed to be the only change while he was in the oxygen room. Subjectively, he was no better.

The second was a girl of 13 with congenital heart disease, later shown by autopsy to be the tetralogy of Fallot, combined with a patent ductus arteriosus. The case is being reported by Dr. Richards²⁹ in further detail elsewhere. It is sufficient to note here that her arterial oxygen saturation, about 60 per cent, was increased only slightly, to 65 per cent, in high oxygen, that there was no change in her carbon dioxide or in her urinary output, that her pulmonary blood flow was practically unaltered, and that subjectively she was not improved. She did not have any edema at any time. She was not in the oxygen room long enough to rule out the possibility of a change in urinary output relative to intake.

II CARDIAC INSUFFICIENCY DEVELOPING AS A SEQUEL TO CHRONIC PULMONARY DISEASE

The effects of oxygen therapy were studied in five cases of cardiac insufficiency due to previous chronic

pulmonary disease two cases of pulmonary tuberculosis, two cases of fibrosis of the lung and one case of emphysema. In these patients, treatment with oxygen was carried on during a period of two to seven months. The tuberculous patients had active tuberculosis with extensive pathology in their lungs. They were both dyspneic at rest, cyanotic, with an elevated temperature and pulse rate. In each instance, residence in the oxygen chamber was followed by increase in comfort, lessened dyspnea, and other evidences of clinical improvement such as increased appetite and lowered pulse rate. In one of them the symptoms of respiratory failure were extreme, and the inhalation of 45 per cent oxygen appeared to prolong life until the acute processes had somewhat subsided. No effect, however, was noted on the progress of the tuberculous lesion itself. In one who had been in the oxygen chamber for two and one-half months a marked rise in arterial carbon dioxide was associated with the increase in the arterial oxygen saturation.

The first patient with fibrosis of the lung was a woman of forty-nine years of age who suffered from progressively extreme dyspnea, marked cyanosis, and paroxysmal coughing for two years. Her respirations were 60 per minute, very shallow, pulse rate 110 without fever. She was kept in an oxygen chamber for six months. During the first month her respirations declined to as low as 28 per minute, pulse to 80 with relief of dyspnea and complete disappearance of coughing. The fibrosis of the lung, however, steadily advanced and it became necessary to give her increasing concentra-

tions of oxygen, from 40 per cent at the start to 55 per cent at the termination of her illness. She died as a result of cerebral thrombosis. A week before her death the arterial oxygen saturation was 89 per cent and the arterial carbon dioxide content had reached the extraordinary figure of 132.1 volumes per cent. (In the cases of congestive heart failure relieved in high oxygen, the arterial carbon dioxide content was elevated from a range of 35 to 40 volumes per cent before oxygen treatment to 45 to 70 volumes per cent after oxygen treatment.) In the second case of fibrosis of the lung which was associated with marked cardiac insufficiency the arterial carbon dioxide content rose from 35.4 volumes per cent to 69.9 volumes per cent and subsequently as improvement in pulmonary function occurred dropped to 48.9 volumes per cent. This patient for a period of five months appeared unable to live without oxygen. Whenever oxygen was discontinued he became dyspneic, cyanotic, and began to accumulate edema fluid. However, at the end of five months oxygen therapy was stopped without recurrence of symptoms of cardiac or respiratory failure. For eight months he was able to go about on restricted activity without distress. At the end of this time slight symptoms of cardiac failure became evident and the patient was put on nasal oxygen for a varying number of hours (2 to 4) during the day.

The patient with emphysema was a man of fifty who suffered from progressive impairment of pulmonary function for a period of seven years. At the time he was seen cardiac insufficiency was so marked as to presage a fatal outcome. He was intensely

cyanotic and dyspneic, gasping at every breath, with a rapid pulse of poor quality. He was treated in an oxygen tent with 50 per cent oxygen for ten days with disappearance of dyspnea and cyanosis. His pulse gradually improved in volume and dropped from 100 to 76. After continuous nasal oxygen at 40 liters a minute through a catheter for one month, nasal catheter treatment was continued for six to eight hours daily, for the following three months. After this period he was able to resume ambulatory activity without oxygen.

III ACUTE CORONARY THROMBOSIS

Dr. Levy and I studied the effects of the administration of 45 per cent oxygen by means of the oxygen tent in four patients suffering from coronary thrombosis. All were critically ill. The following observations were made in these cases:

1. Subjective improvement occurred in from one to three hours after the administration of oxygen was begun. This manifested itself chiefly by relief of respiratory embarrassment and restlessness.

2. Cyanosis was diminished or abolished.

3. The respiratory rate was slowed and Cheyne-Stokes breathing, if present, tended to disappear.

4. The heart rate became slower. The heart sounds grew stronger and the volume of the pulse improved.

5. Removal of the oxygen tent before satisfactory readjustment of circulatory conditions had taken place resulted in a recurrence of the symptoms and signs just enumerated.

In sudden thrombotic closure of a branch of the coronary artery there results an abrupt interference with the blood supply of the heart which induces an initial state of shock. The degree of functional disturbance that follows depends on the caliber and location of the occluded vessel, as well as on the distribution and anastomoses of the coronary system in the affected individual. If the resulting area of myocardial infarction is large, signs and symptoms of congestive heart failure may ensue. The cardiac action becomes weak, rapid and often irregular. The blood pressure falls sharply and remains at a relatively low level. Cyanosis appears, and moist râles are heard at the bases of the lungs. Respiration is accelerated and difficult. The picture is one of acute oxygen-want due to myocardial insufficiency.

Employment of oxygen therapy (preferably in a concentration of from 45 to 50 per cent) may aid in maintaining an adequate circulation until the heart has had an opportunity to recover from its acute functional disturbance. Obviously, the cardiac injury may be so severe that recovery is impossible. But in some instances effective use of oxygen may be responsible for the saving of life.

The responses of the cases studied allow the conviction that anoxemia and its treatment may play a crucial rôle in determining the outcome after coronary thrombosis.

IV CORONARY ARTERIOSCLEROSIS WITH CHRONIC CARDIAC PAIN

I have recently studied three cases of coronary arteriosclerosis with chronic cardiac pain in men in the fifth

and sixth decades of life. All these patients had one to five attacks of cardiac pain daily at rest in bed before treatment with oxygen. They were treated by residence in the oxygen chamber with 50 per cent oxygen for a period of two weeks. In the first, which was the most severe, the attacks gradually decreased in number and severity, but promptly recurred when the patient was removed from the chamber. His condition was at all times exceedingly grave and he died three weeks after removal from the oxygen chamber. In the second case the attacks of pain gradually disappeared. After removal from the oxygen room the pains recurred to a slight extent but permitted the patient to return home. During the following six months he has been markedly improved over his previous condition, having only a comparatively small number of attacks of mild pain, i.e., two to three attacks a month, none of them requiring more than rest and nitroglycerin.

The third patient was less severely affected than the others, averaging one attack of pain daily at rest in bed in the hospital before admission to the chamber. During ten days residence in 45 per cent oxygen he had one attack of pain, and felt extremely well. For six weeks after he was able to resume restricted activity without pain. At that time, however, pain recurred waking him up during the night. He was placed on nasal oxygen, 40 liters per minute for eight hours a day for six weeks and since that time, a period of four months, he has had only occasionally mild pain on activity and is not awakened at night by cardiac pain.

DISCUSSION

The improvement which was evident in the cases of acute coronary thrombosis after inhalation of 45 to 50 per cent oxygen indicates the importance of the factor of oxygen-want in this condition. After coronary closure there is first a pronounced anoxemia of the heart muscle, followed by anoxemia in the venous blood as a result of the impaired heart action and, very soon after, an arterial anoxemia due to the development of passive congestion and edema of the lungs. The inhalation of 45 to 50 per cent oxygen tends to remove the arterial anoxemia and prolong life until the heart is able to compensate, if it is possible to do so, for its acute disturbance in function. The prompt collapse which follows withdrawal of oxygen before the heart muscle has adapted itself to the closure makes manifest the significance of arterial anoxemia in the symptomatology of the disease.

The problem of interpreting the origin of cardiac pain is complicated by the fact that no afferent nerve fibres are to be found in the heart muscle or its blood vessels. The possibility is present that supposedly efferent sympathetic nerves in the heart muscle may carry afferent impulses. Wiggers¹¹ observes in a recent review that although "Sir Clifford Allbutt maintained to the end of his life that cardiac angina could arise only from stimulation of the nerve fibres terminating in the outer coats of the aorta, a great deal of clinical and even a little experimental evidence exists that anoxemia of the heart muscle—regardless of whether it is produced by cor-

onary embolism, thrombosis or sclerosis —is capable of inaugurating serious attacks of cardiac pain" That local anoxemia of the heart muscle may produce pain is certainly suggested by the relief of pain in the three cases of coronary arteriosclerosis who were treated in the oxygen room

Although we cannot entirely explain the mechanism by which relief of pain occurs in cases of coronary arteriosclerosis without cyanosis or evident anoxemia, we have obtained some knowledge that bears on the problem. In the first place, the inhalation of 50 per cent oxygen in normal men we have found capable of raising the arterial oxygen saturation from 95 to 99 per cent. In one of the cases of coronary arteriosclerosis which we measured, the arterial oxygen saturation was raised from 94 to 99 per cent. Although this represents a small increase in per cent saturation, it indicates a very considerable rise in the tension or partial pressure of oxygen available to the tissues (because of the shape of the oxygen dissociation curve), and provides therefore a possible explanation for relief of local anoxemia in the heart muscle. The inhalation of high concentrations of oxygen causes the normal heart to beat at a slower rate,³⁰ and affects more markedly the heart in cardiac insufficiency,^{12,24} which suggests a lessened strain due to a greater oxygen supply.

The most interesting and striking effects of oxygen therapy in the cases of cardiac insufficiency, both those due to local disease of the heart itself and those in which heart failure appeared to be secondary to primary pulmonary

disease are (1) Relief of dyspnea and orthopnea, (2) elevation of the arterial carbon dioxide content and of the level of the carbon dioxide dissociation curves, and (3) diuresis.

1. The relief of dyspnea which frequently manifests itself within several hours after removal to an oxygen-enriched atmosphere indicates that oxygen-want plays a decisive rôle in the production of cardiac dyspnea. We may briefly review at this point some of the known factors involved in the production of shortness of breath in cardiac insufficiency.

Passive congestion and edema in the lungs was noted by von Basch³² as resulting in a stiffening of the lung with consequent impairment of the expansile capacity of the lungs, or vital capacity. Siebeck³³ also found that the lung expands unequally in cardiac insufficiency and thus makes for an imperfect mixture of the gases in the lung, with resultant impairment of normal diffusion of oxygen. In addition to these difficulties in moving the lung, there must also be a decreased diffusion capacity of the swollen alveolar membrane for respired gases especially oxygen. The end result of pulmonary dysfunction is insufficient oxygen saturation of the arterial blood. This involves all the tissues in the consequences of anoxemia, many of which have been noted in the introduction. An additional one may be commented upon at this point, namely lactic acid accumulation (Araki³⁴) (MacLeod³⁵). An accumulation of lactic acid is of particular interest with reference to the respiratory center. At the present time the most satisfactory explanation of the respiratory stimulus

is that it is governed by the acidity of the tissue of the respiratory center (Douglas and Haldane³⁶), (Winterstein³⁷), (Gesell³⁸)

When in our cases the clearing of arterial anoxemia resulted from the inhalation of 45 to 50 per cent oxygen, dyspnea was relieved and gradually disappeared. It is evident (1) that the difficulties in oxygen absorption resulting from lung stiffening, decreased vital capacity and swollen alveolar membranes were overcome, and (2) that the increased oxygen saturation of the pulmonary blood tends to diminish tissue acid accumulation. In the one case measured, the blood lactic acid rapidly returned to normal following the inhalation of oxygen. That the respiratory stimulus was thereby decreased is evidenced by the lowered pulmonary ventilation and that there was some diminution in general tissue acidity was suggested by the small but constant lowering of arterial H-ion concentration which we observed.

The difficulty of eliminating carbon dioxide has also been stressed as an important factor in the causation of cardiac dyspnea, which brings us to the second result of oxygen therapy to be discussed.

2 The marked rise in carbon dioxide content of the arterial blood was constantly associated with (1) clinical improvement, (2) increased arterial oxygen saturation, and (3) impairment of pulmonary function in respect to the absorption of oxygen.

If the inhalation of oxygen-enriched air makes possible a lower pulmonary ventilation it is obvious that an increase in blood carbon dioxide levels

and hence in alveolar air will permit the elimination of a greater amount of carbon dioxide with a lower pulmonary ventilation. In the cases of congestive failure due to primary cardiac disease the arterial carbon dioxide content was elevated from a range of 35 to 40 volumes per cent to 45 to 70 volumes per cent, after oxygen treatment. This increase in the carbon dioxide levels in the blood did not, however, represent a carbon dioxide acidosis due to deficient elimination of carbon dioxide, since the H-ion concentration of the blood was never more acid but on the contrary, tended to be slightly less acid when the carbon dioxide became elevated. It is therefore evident that carbon dioxide diffuses through the lungs in higher concentrations when anoxemia and its consequences are relieved. This fact necessitates an alteration in the conception of previous investigators concerning the rôle of carbon dioxide in the causation of cardiac dyspnea.

Wiggers¹¹ remarks in a recent review of the physiology of cardiac dyspnea that "Neither an excess of carbon dioxide, as in exercise, nor the existence of a fixed acidosis is separately responsible for the dyspnea. But a moderate grade of fixed acidosis combined with pulmonary congestion which prevents the compensatory elimination of carbon dioxide might easily produce augmented breathing in heart disease. In the light of this conception, also, it appears to be a basic fact that impairment of the pulmonary circulation is the ultimate cause that prevents the free compensatory elimination of carbon dioxide."

Our studies, however, indicate that lack of oxygen plays the primary rôle in the production of cardiac dyspnea. Passive congestion of the alveolar membranes of the lung and the associated decreased vital capacity impair, first of all, the diffusion of oxygen into the pulmonary veins, resulting in arterial anoxemia and the consequences of oxygen-want in the tissues, such as accumulation of lactic acid. When the anoxemia is relieved, there is a constant and marked rise in the carbon dioxide concentration of the blood with an *even greater elimination* of carbon dioxide per breath through the congested lung. Thus, in one of the cases of congestive failure, the carbon dioxide content of the arterial blood rose from 38.4 to 69.9 volumes per cent in four days. It appears, therefore, likely that the elevation in carbon dioxide level in the blood is an adaptive change which is readily accomplished if sufficient oxygen is supplied to maintain normal metabolic activity. Also, lactic acid accumulation disappears when anoxemia is relieved. It seems probable that base to retain carbon dioxide is in part derived from the blood lactates in this manner. A decrease in pulmonary ventilation follows with a lessened sense of pulmonary effort and therefore relief of dyspnea.

To summarize, then, cardiac dyspnea was relieved (1) by the provision of an adequate oxygen supply to the tissues, (2) by the development of a mechanism of eliminating carbon dioxide by increasing the concentration in the blood, and (3) by the oxidation of an excessive accumulation of lactic acid in the blood.

We may consider now the general factor involved in the increase in blood carbon dioxide which follows oxygen treatment in the cases of cardiac failure as well as in the cases of chronic pulmonary disease. This appears to be the extent of impairment of pulmonary function in respect to the absorption of oxygen. In the patient with fibrosis of the lung in whom a progressive impairment of the function of the lung took place so that 55 per cent oxygen became necessary to support life, the blood carbon dioxide reached 132.1 volumes per cent. It would appear that this extraordinary high concentration of carbon dioxide in the alveolar air represented a mechanism capable of eliminating carbon dioxide in the presence of an extreme diminution of lung function. In the second patient with fibrosis of the lung and cardiac insufficiency, the carbon dioxide in the arterial blood rose from 38.4 to 69.9 after four days' oxygen treatment, and then, as the patient improved, dropped to 48.9 volume per cent, even though he was still breathing an oxygen-enriched atmosphere. Thus, when the function of the lung, if severely impaired, was relieved by the inhalation of oxygen, the carbon dioxide concentration in the blood and in the alveolar air became elevated, as an adaptive reaction noted above. But when the pulmonary function improved in respect to the absorption of oxygen, the carbon dioxide concentration in the blood and alveolar air diminished.

Although the carbon dioxide in the blood declines after clinical improvement has taken place whether the patient is breathing oxygen or air, a slight increase in blood carbon dioxide

may still persist in a high oxygen atmosphere. It has been noted in animals kept in oxygen-enriched atmospheres that an increase in carbon dioxide tension in the tissues occurs (Campbell²²). The significance of the elevation in carbon dioxide in normal animals exposed to high oxygen is not clear. As far as our purposes are concerned, the rise in carbon dioxide following oxygen treatment in patients suffering from dyspnea appears to be an adaptive mechanism for eliminating carbon dioxide, accompanied by a decreased pulmonary ventilation which is made possible only by the relief of anoxemia and its consequences.

3 The diuresis and disappearance of edema was a marked feature of four of our cases. The physiologic explanation of cardiac edema is itself by no means clear, but three factors have been described: (1) edema of the dependent parts due to stasis and physical filtration, (2) impairment of renal function due to congested glomerular membranes, and (3) altered permeability of capillaries due to anoxemia⁴¹. Oxygen therapy resulted in an improved state of the circulation which would tend to remove the edema due to stasis as well as relieve the passively congested glomerular membranes. In so far as the tissue cells of the body are altered in their permeability due to anoxemia, an increased supply of oxygen would likewise be beneficial. Other alterations in tissue water balance may also be implicated concerning which our data give no information.

I am conscious that this discussion of the therapeutic use of oxygen in heart disease displays many large gaps in our knowledge. It is our hope,

however, that these observations will stimulate further studies in which effective and comfortable methods of administering oxygen will fulfil the prophecy of Priestley shortly after he had discovered oxygen 157 years ago.

"My reader will not wonder", says Priestley,⁴² "that, after having ascertained the superior goodness of dephlogisticated air (that is, oxygen), by mice living in it and by the other tests above mentioned, I should have the curiosity to taste it myself. I have gratified that curiosity by breathing it, drawing it through a glass syphon, and by this means I reduced a large jar full of it to the standard of common air. The feeling of it to my lungs was not different from common air, but I fancied that my breath felt peculiarly light and easy for some time to come. Who can tell but that in time this pure air may become a fashionable article in luxury? Hitherto only two mice and myself have had the privilege of breathing it."

SUMMARY

The therapeutic use of oxygen was studied in eight patients with congestive heart failure due to primary cardiac disease, in five cases of cardiac insufficiency developing as a sequel to chronic pulmonary diseases, in four cases of acute coronary thrombosis and in three cases of coronary arteriosclerosis with chronic cardiac pain.

In the cases of congestive heart failure the most striking effects observed were (1) relief of dyspnea and orthopnea, (2) diuresis and disappearance of edema, and (3) a marked rise in the carbon dioxide content of the arterial blood. Other observations noted were relief of cyanosis, in

creased arterial oxygen saturation, decreased pulmonary ventilation, lowered pulse rate and decrease in blood lactic acid

In the cases of acute coronary thrombosis life appeared to be prolonged by the inhalation of an oxygen-enriched atmosphere until the heart was able to recover from its acute functional disturbance. The cases of coronary arteriosclerosis with chronic cardiac pain were relieved by residence in a high oxygen atmosphere

These results indicate that oxygen-want plays the primary rôle in the production of many forms of cardiac dyspnea. The increase in carbon dioxide content of the arterial blood occurs as an adaptative change which facilitates the elimination of carbon dioxide

The clinical improvement which patients suffering from the various forms of heart failure experience suggests a new employment of oxygen therapy by effective methods in these conditions

BIBLIOGRAPHY

- ¹VÖR, C Ueber die Entwicklung der Lehre von der Quelle der Muskelkraft und einiger Theile der Ernährung seit 25 Jahren, *Ztschr f Biol*, 1870, vi, 305-401
- ²PFLUGER, E Ueber die Diffusion des Sauerstoffs, den Ort und die Gesetze der oxydations Prozesse im thierischen Organismus, *Arch f Physiol*, 1872, vi, 43-64
- ³HIGGINS, H L, and BENEDICT, F G Some energy factors of the urine excreted after severe muscular exercise, *Am Jr Physiol*, 1911, xxviii, 291-300
- ⁴HALDANE, J S *Respiration*, 1922, Yale University Press, New Haven
- HALDANE, J S, KELLAS, A M, and KENNAWAY, E L Experiments on acclimatization to reduced atmospheric pressure, *Jr Physiol*, 1919, liii, 181-206
- ⁵BARCROFT, J, COOKE, A, HARBIDGE, H, PARSONS, T R, and PARSONS, W Flow of oxygen through pulmonary epithelium, *Jr Physiol*, 1920, liii, 450-472
- BARCROFT, J Anoxemia, *Lancet*, 1920, ii, 485-489
- ⁶VON TERRAY, P Ueber den Einfluss des Sauerstoffgehaltes der Luft auf den Stoffwechsel, *Arch f Physiol*, 1897, lxxv, 393-446
- ⁷SCHNEIDER, E C, TRUESDELL, D, and CLARKE, R W Respiratory changes during and after period of anoxemia, *Am Jr Physiol*, 1925, lxxxi, 714-728
- ⁸KROGH, A The respiratory exchange of animals and man, 1916, Longmans, Greene and Co, London
- ⁹MEANS, J H, and NEWBURGH, L H Studies of the blood flow by the method of Krogh and Lundhard, *Tr Assoc Am Phys*, 1915, xxx, 51-62
- ¹⁰LUNDGAARD, C Studies of oxygen in the venous blood, *Jr Exp Med*, 1918, xxvii, 179-247
- ¹¹HARROP, G A The oxygen and carbon dioxide content of arterial and venous blood in normal individuals and in patients with anemia and heart disease, *Jr Exper Med*, 1919, xxx, 241-257
- ¹²BARACH, A L, and WOODWELL, M N Studies in oxygen therapy with determination of blood gases 1 In cardiac insufficiency and related conditions, *Arch Int Med*, 1921, xxviii, 367-393
- ¹³BEDDARD, A P, and PEMBREY, M S Observations on pulmonary ventilation in disease, *Brit. Med Jr*, 1908, ii, 580-583
- ¹⁴FITZGERALD, M P The alveolar carbonic acid pressure in diseases of the blood and in diseases of the respiratory and circulatory systems, *Jr Path and Bact*, 1909-10, xiv, 328-343
- ¹⁵PORGES, O, LEIMDORFER, A, and MARKOVICI, E Ueber die Kohlensäurespannung des Blutes in pathologischen Zuständen II Ueber die Kohlensäurespannung des Blutes in der kardialen und pulmonalen Dyspnoe, *Ztschr f klin Med*, 1913, lxxvii, 446-470
- ¹⁶PEABODY, F W Studies on acidosis and dyspnea in renal and cardiac disease, *Arch Int Med*, 1914, xii, 236-262

- ¹⁷PETERS, J P, and BARR, D F Carbon dioxide absorption curve and carbon dioxide tension of blood in cardiac dyspnea, Jr Biol Chem, 1921, xlv, 537-595
- PETERS, J P, BULGER, H. A, and EISEMAN, A J Studies on carbon dioxide absorption curve of human blood, Jr Biol Chem, 1923, lviii, 747-791
- ¹⁸CAMPBELL, J M H, POULTON, H, POULTON, R, and POULTON, E P. The relation of oxyhemoglobin to carbon dioxide of blood, Jr Physiol, 1920, liv, 152-166
- ¹⁹CAMPBELL, J M H, and POULTON, E P Effect on breathless subjects of residence in oxygen chamber, Quart Jr Med, 1927, xx, 141-172
- ²⁰BEDDARD, A P, and PEMBREY, M S Observations on pulmonary ventilation in disease, Brit Med Jr, 1908, ii, 580-583
- ²¹CAMPBELL, J M H, HUNT, G H, and POULTON, E. P Examination of blood gases and respiration in disease with reference to cause of breathlessness and cyanosis, Jr Path and Bact, 1923, xxvi, 234-296
- ²²CAMPBELL, J A Prolonged alterations of oxygen pressure in the inspired air with special reference to tissue oxygen tension, tissue carbon dioxide tension and hemoglobin, Jr Physiol, 1927, lxii, 211-231
- ²³BAKER, B M Effect of cardiac rate and inhalation of oxygen on transient bundle branch block, Arch Int Med, 1930, xlv, 814-822
- ²⁴BARACH, A L, DICKINSON, R W, MILHORATO, A T, and LEVY, R L Effects of oxygen therapy on patients with congestive heart failure, Proc Soc. Exper Biol and Med, 1930, lviii, 308-310
- BARACH, A L. and RICHARDS, D W Effects of treatment with oxygen in cardiac failure, Arch Int Med, 1931, lviii, 325
- ²⁵LEVY, R L, and BARACH, A L Therapeutic use of oxygen in coronary thrombosis, Jr Am Med Assoc, 1930, xcii, 1363-1365
- ²⁶BARACH, A L New type of oxygen chamber, Jr Clin Invest, 1926, ii, 463-476
- BARACH, A L. New oxygen chamber ventilated by thermal circulation of air, Mod Hosp, 1929, xxxii, 144-148
- ²⁷BARACH, A L. A new oxygen tent, Jr Am Med. Assoc, 1926, lxxxvii, 1213-1215
- ²⁸BARACH, A L. Administration of oxygen by nasal catheter, Jr Am Med Assoc, 1929, xciii, 1550-1551
- ²⁹RICHARDS, D W, RILEY, C B, and HISCOCK, M Congenital heart disease,—Measurement of the circulation, 1931, xlvii, 484-500
- ³⁰BENEDICT, F G, and HIGGINS, H L Effects on men at rest of breathing oxygen-rich gas mixtures, Am Jr. Physiol, 1911, xxviii, 1-28
- ³¹WIGGERS, C J Physiologic meaning of common clinical signs and symptoms in cardiovascular disease, Jr Am Med Assoc., 1931, xcvi, 603-610
- ³²VON BASCH, S Klinische und experimentelle Studien aus dem Laboratorium, 1891-1896, A Hirschwald, Berlin
- ³³SIEBECK, R. Ueber kardiaale Dyspnoe, Klin Wchnschr, 1929, viii, 2121-2125
- ³⁴ARAKI, T Ueber die Bildung von Milchsäure und Glycose in Organismus bei Sauerstoffmangel, Ztsch f physiol Chem, 1891-2, xvi, 453-459
- ³⁵MACLEOD, J J R Concentration of lactic acid in blood in anoxemia and shock, Am Jr Physiol, 1921, lv, 184-196
- ³⁶DOUGLAS, C G, and HALDANE, J S. The regulation of normal breathing, Jr. Physiol, 1909, xxviii, 420-440
- ³⁷WINTERSTEIN, H. Die Reaktionstheorie der Atmungsregulation, 1921, clxxxvii, 293-298
- ³⁸GESELL, R., and HERTZMAN, A B. The regulation of respiration, Am Jr Physiol, 1926, lxxxviii, 610-629
- ³⁹KROGH, A The anatomy and physiology of capillaries, 1922, Yale University Press, New Haven
- ⁴⁰LANDIS, E M Micro-injection studies of capillary permeability, Am Jr. Physiol, 1927-28, lxxxiii, 528-542
- ⁴¹PRIESTLY, JOSEPH Experiments and observations on air. 1776

The Reaction to Nitrites in the Anginal Syndrome and Arterial Hypertension*

By ALEX M. BURGESS, M.D., F.A.C.P., *Providence, R. I.*

SINCE the introduction of the use of amyl nitrite by Sir Lauder Brunton in 1867 nothing has been found to excel the nitrites for the relief of the pain in angina pectoris. Although the pharmacology of the members of this group has been exhaustively studied the question as to the mode of their action in anginal pain has never been definitely settled. This is due partly to the fact that the cause of the pain has not been thoroughly understood. Furthermore, because of their known action on the walls of the peripheral arterioles resulting in a lowering of blood pressure, the nitrites have been used in attempts to cause either temporary or permanent lowering of the pressure in patients suffering from arterial hypertension and are therefore of interest to the clinician. The relaxability of the walls of the arterioles as measured by the drop in diastolic pressure after the inhalation of amyl nitrite has also been studied in an attempt to estimate the prognosis in these cases¹. It has seemed worth while, therefore, to make a series of simple clinical tests by means of repeated blood pressure esti-

mations of the reaction which the rapidly acting drugs, amyl nitrite and nitroglycerine produce in three types of people—the normal, those with arterial hypertension and those who are suffering from attacks of the so-called “ambulatory” angina pectoris.

No attempt will be made to enter into an exhaustive discussion of the pharmacology of the nitrite group. The familiar text book description mentions the flushing of the face, headache, and tachycardia after the inhalation of amyl nitrite, and the rapid fall in blood pressure due to a direct action on the smooth muscle cells of the walls of the arterioles and veins. A similar but less rapid effect is attributed to nitroglycerine. Anyone who has tested the amyl nitrite on himself can bear witness to the very unpleasant nature of the subjective symptoms produced in a normal person. That the tachycardia is due to vagus action has been shown, as it does not occur in experimental animals if the nerve has been severed. It has been amply demonstrated that the fall in pressure is due to a direct action on the vessel walls.

The statement is common that in hypertension generally the action of amyl nitrite and nitroglycerine is to

*Presented at the Baltimore Meeting of the American College of Physicians, March 24, 1931

produce a sharp and temporary fall in blood pressure² although no detailed studies of this action on systolic and diastolic pressure are available. Stieglitz³ has recently emphasized the importance of a fall in diastolic pressure in these cases after the inhalation of amyl nitrite as indicating that the peripheral arterioles have not yet reached an advanced state of sclerosis and therefore that the prognosis may still be favorable. He recommends that the pressure be taken at the height of the symptoms; flushing, tachycardia, etc., and that the proportion of the distance that the diastolic has fallen toward 90 mm. be taken as the indication of arteriolar relaxability.

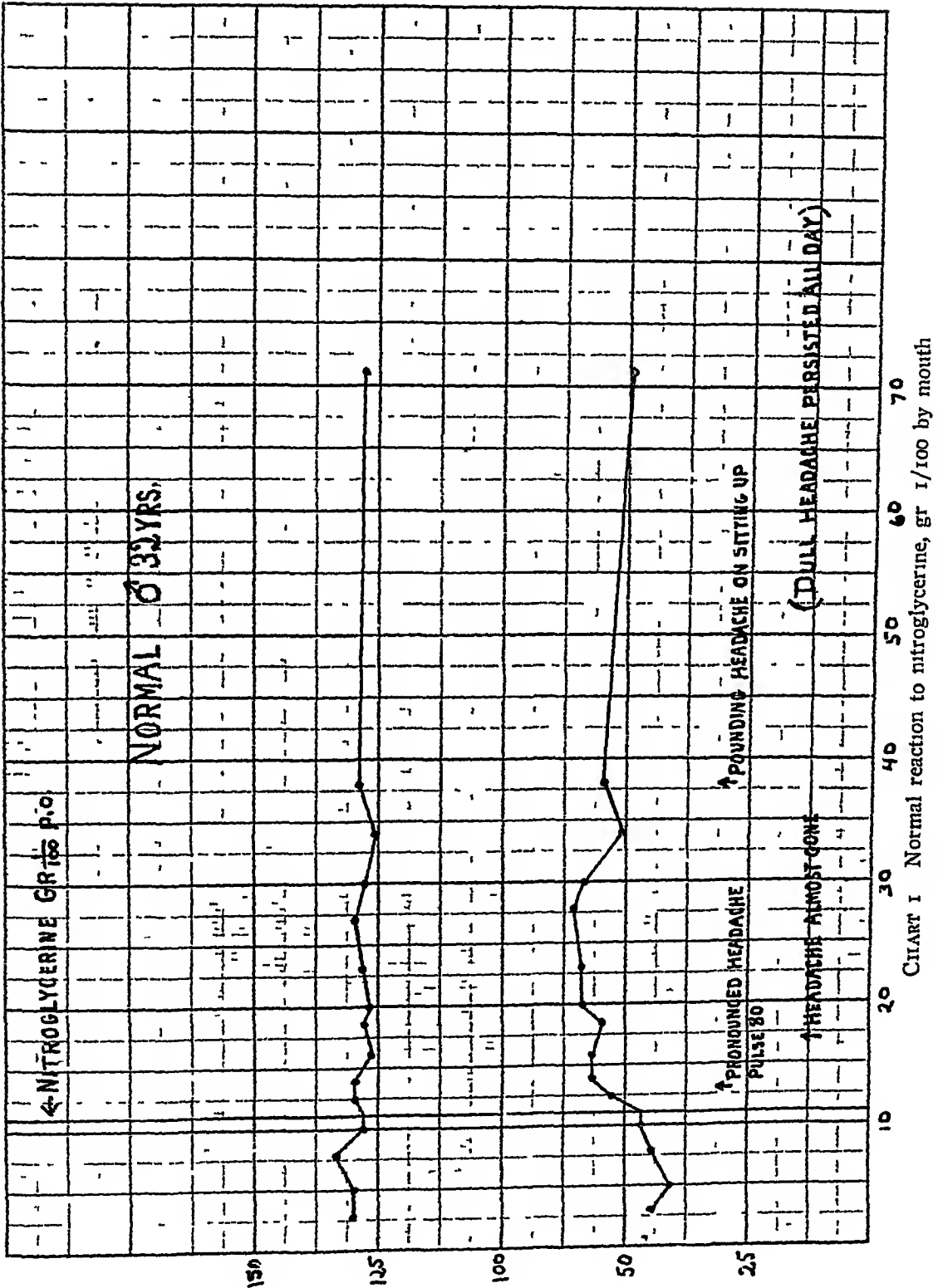
The action of the nitrites on the cerebral circulation is of especial interest to those who have attempted to relieve headache in cases of arterial hypertension by their use. It has been clearly shown⁴ that the pial vessels are dilated by these drugs and that intracranial pressure is increased⁵. The writer has seen a severe headache in a patient with marked arterial hypertension made almost intolerable by a dose of 1/100 gram of nitroglycerine which, by the way, had no appreciable effect on the blood pressure (see Chart 4).

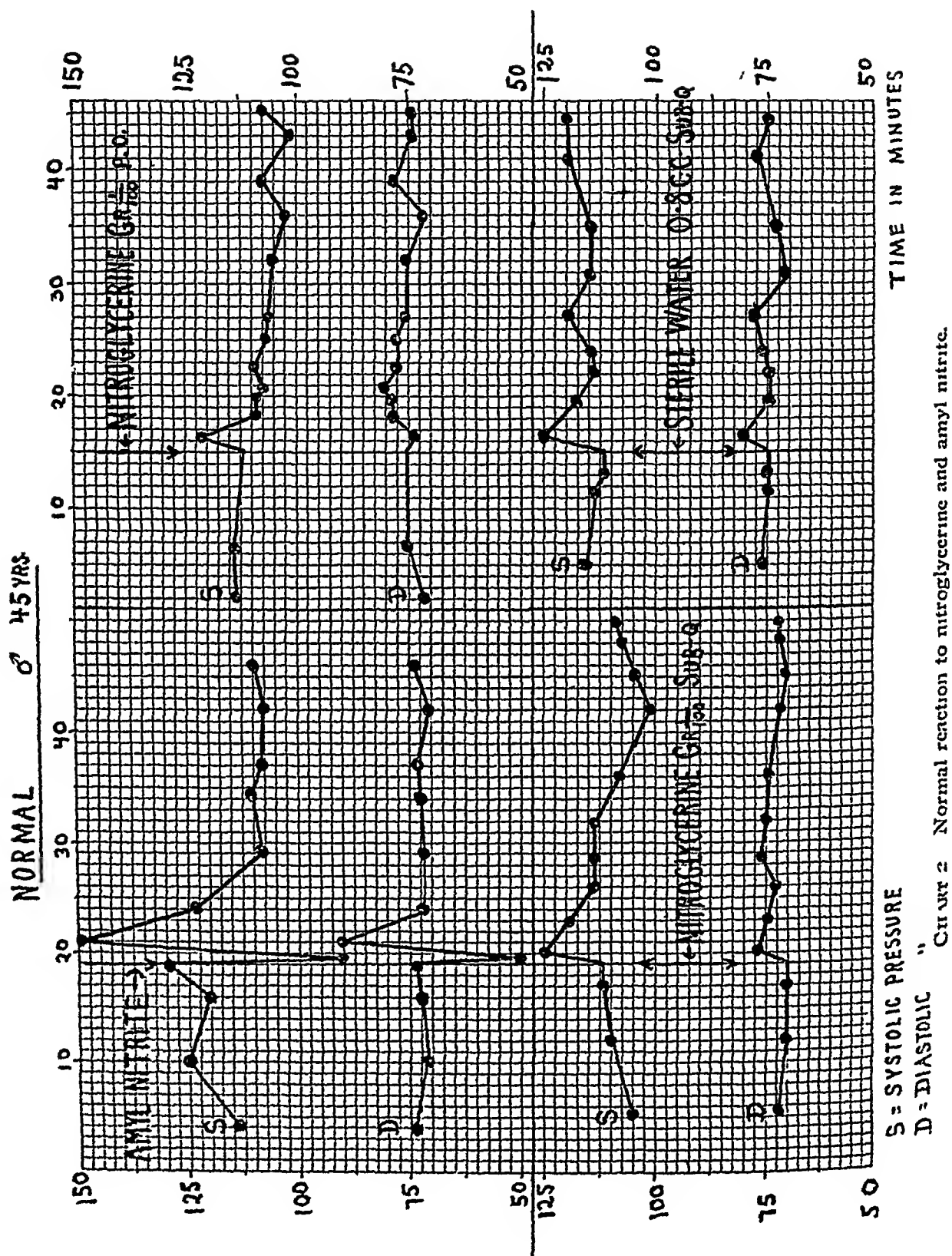
The effect of the nitrites on the pulmonary circulation is apparently the opposite of that on the general circulation. Isolated strips of pulmonary artery have been noted to contract when in contact with the nitrites⁶ and a rise in pulmonary pressure has been demonstrated after their use.

As regards the coronary arteries

the statement is made that they also are dilated as are other peripheral arteries. Dilation of isolated rings of coronary artery⁷ and increased outflow from the coronary veins have been shown to be the result of nitrite action by some observers,⁸ while others have been unable to produce experimentally, any definite evidence of such action⁹. Perhaps, however, the best demonstration of the effect on the coronaries is that by Smith¹⁰ who showed in dogs' hearts in which artificial infarction had been produced by ligation of the coronary branches an actual decrease in the cyanosis of the infarcted areas due to increased collateral circulation following the intraventricular injection of 1/200 grain of nitroglycerine.

The demonstration of an increase in coronary flow by the nitrites is of great importance in upholding the view that the pain in angina pectoris is caused by ischemia of the heart muscle, so ably championed by Keefer and Resnik¹¹. These investigators are, however, very sceptical as to the likelihood of "coronary spasm" as a usual origin of the pain. Whatever may be the cause of the ischemia, it is safe to say that if this ischemia is the cause of the pain, dilation of the coronary arteries seems a reasonable mechanism of its relief. If, on the other hand, a tendency to stasis in the first part of aorta and in the coronaries is the cause of the pain, as believed by May¹², then, as he says, the dropping of the diastolic pressure by the nitrites is a reasonable mechanism for its relief. The following studies do, it is believed, throw some light on this question.





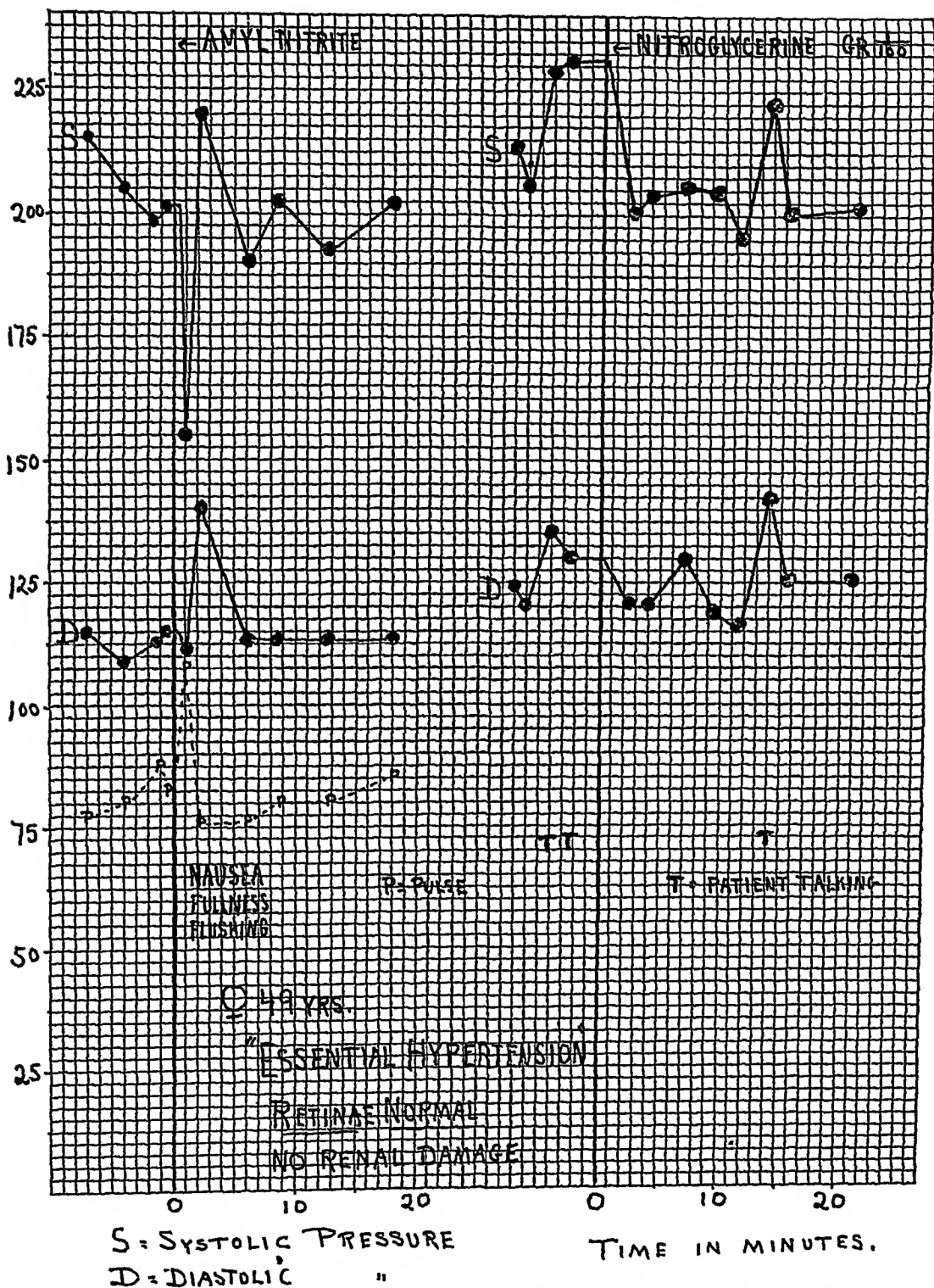


CHART 3 Arterial hypertension. Note absence of fall in diastolic pressure after amyl nitrite in spite of normal retinal vessels and kidneys

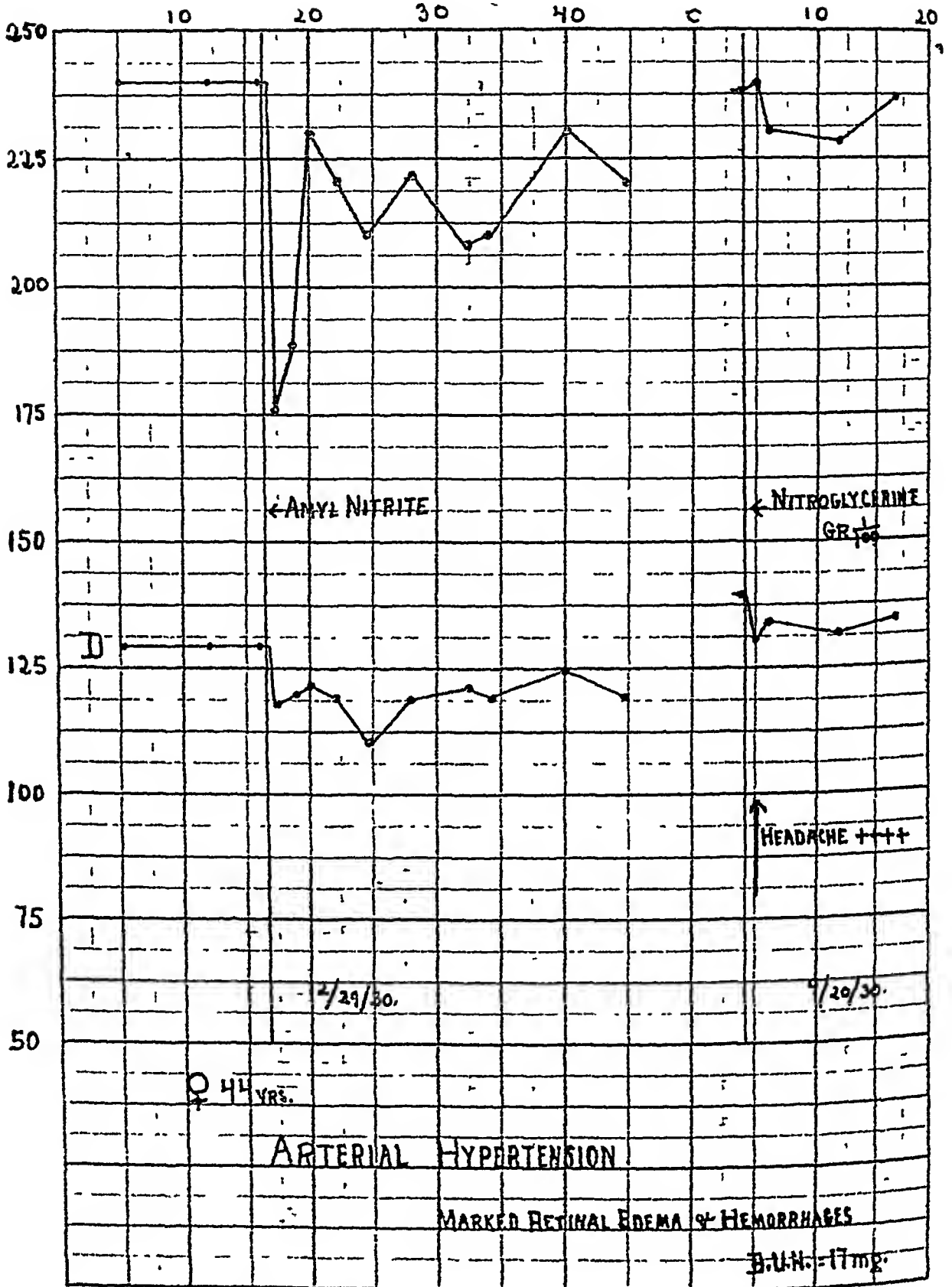


CHART 1. Arterial hypertension, severe, with marked retinal edema. Note increase in headache following nit-glycerine without fall in blood pressure

THE REACTION IN THE NORMAL HUMAN BEING

A few preliminary tests were made on normal persons. As Charts 1 and 2 demonstrate, the action was found to be as follows: (1) After nitroglycerine (either 1/100 or 1/50 grain dissolved in the mouth or gr 1/100 subcutaneously) no immediate fall in blood pressure was noticed although there was a general tendency for the systolic pressure to fall during the next few minutes. Such a general decrease is also often noted in normal people with rest alone. No fall in diastolic pressure was noted. (2) After amyl nitrite an abrupt fall occurred in 30 seconds in both systolic and diastolic pressure. This was followed by a quick compensatory rise in both systolic and diastolic pressure sometimes to points above the original readings. After two minutes the pressure was not much different from that observed at the start and no further effect was noted except in some instances a slight tendency downward on the part of the systolic pressure. (See Chart 2.)

THE REACTION IN ARTERIAL HYPERTENSION

(1) Following the administration of nitroglycerine gr 1/100 or 1/50 by mouth the majority of the sixteen patients studied by this method showed no constant effect on either systolic or diastolic pressure although a fall occurred in some instances. As a comparable fall is often noted¹³ with rest alone it is probable that in these patients the lowering of pressure was due to the rest rather than to the drug. (Charts 3, 4, 5 and 9.) (2)

After amyl nitrite in the twelve patients investigated, the same sudden drop was seen in systolic pressure as was noted in normals, but the subsequent rise did not as a rule reach the original height. The diastolic pressure fell markedly in some and not at all in others. It is worth noting that the fall in pressure after amyl nitrite is so rapid (occurring in 15 to 30 seconds) and that the compensatory rise occurs so quickly (1 to 2 minutes) that it is never possible to be sure that one has found the low point and in many instances this must have been missed. With regard to subjective symptoms it was found that these varied greatly in their severity and that neither their severity nor the time of their occurrence had any relation to the presence or absence of the fall in systolic or diastolic pressure. Furthermore, the presence or absence of a marked blood pressure fall could not be shown to have any definite relation to retinal arteriosclerosis or evidence of renal damage, as the charts demonstrate. Charts 3, 4, 6, 7, 8 and 9.)

THE REACTION IN ANGINA PECTORIS

Before reporting the results of the reactions noted after the use of nitrites in attacks of so called "ambulatory" angina pectoris, it is perhaps worth noting that in every one of the eight patients studied the pressure during the attack and before treatment was instituted was found to be well above the usual pressures noted in these persons when they were free from attacks. This is contrary to the experience of Harlow Brooks

in these cases¹⁴ but in accord with the writer's previous experience.

(1) The action of nitroglycerine was studied in fifteen attacks occurring in eight patients following 1/200 to 1/50 gr. by mouth. No change or a slight rise in systolic pressure occurred within the first minute. Usually within three minutes a marked drop in systolic and a slight drop in diastolic pressure took place. The maximum drop in systolic and diastolic pressure usually occurred within ten

minutes (Charts 10, 11, 12, 14, 15 and 16)

Relief in Pain Partial relief of pain ordinarily was noted in from one to two minutes, and complete relief except for residual soreness at times occurred within a minute and a half, and if the dose had been sufficient to control the situation had usually been established before the end of five minutes. It was evident that considerable or occasionally complete relief of pain took place in some cases before

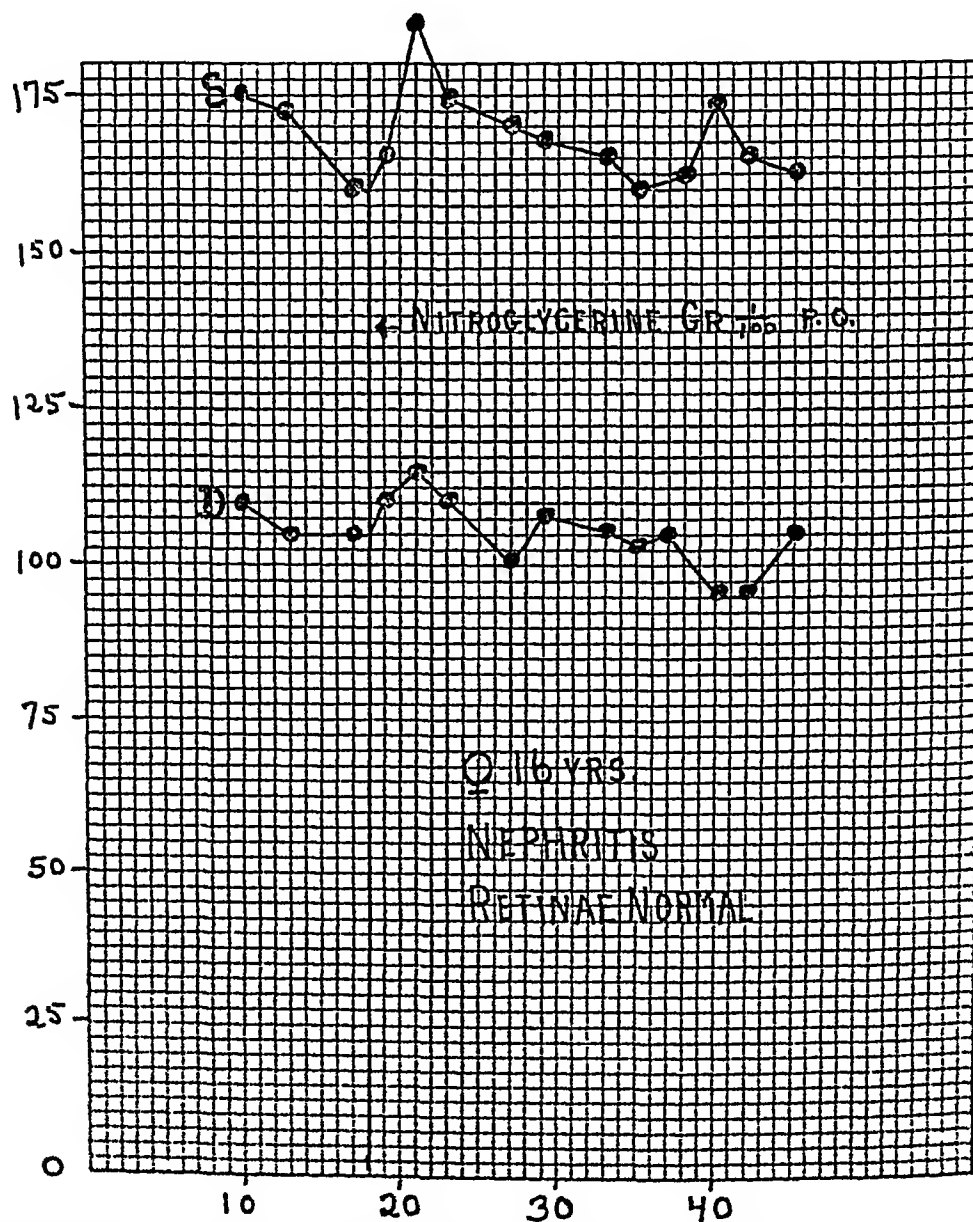


Chart 5. Nephritis with hypertension in a 16 year old girl. Note lack of response to nitroglycerine.

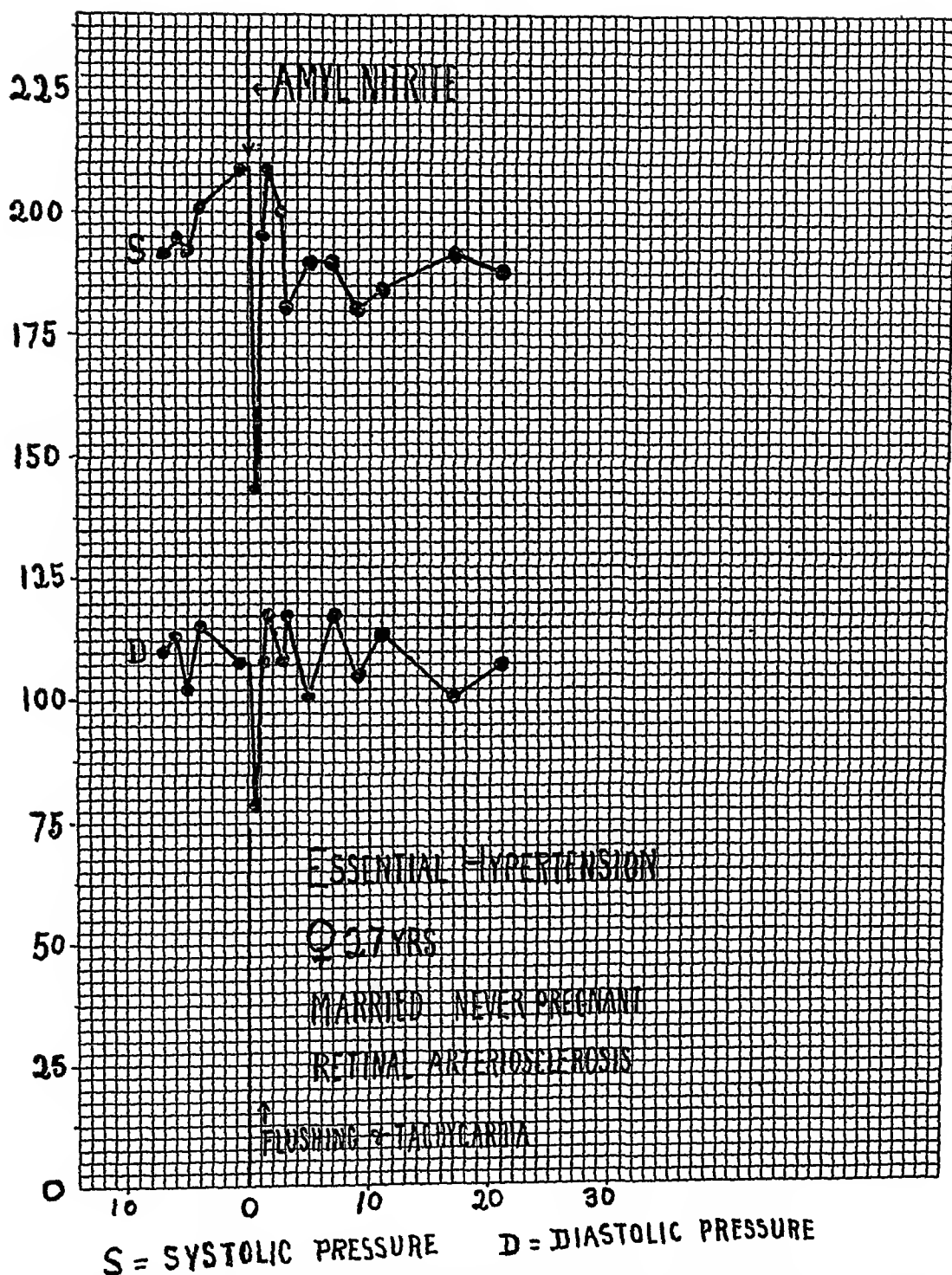


CHART 6 Arterial hypertension. Note marked fall in pressure after amyl nitrite in spite of evidence of retinal arteriosclerosis

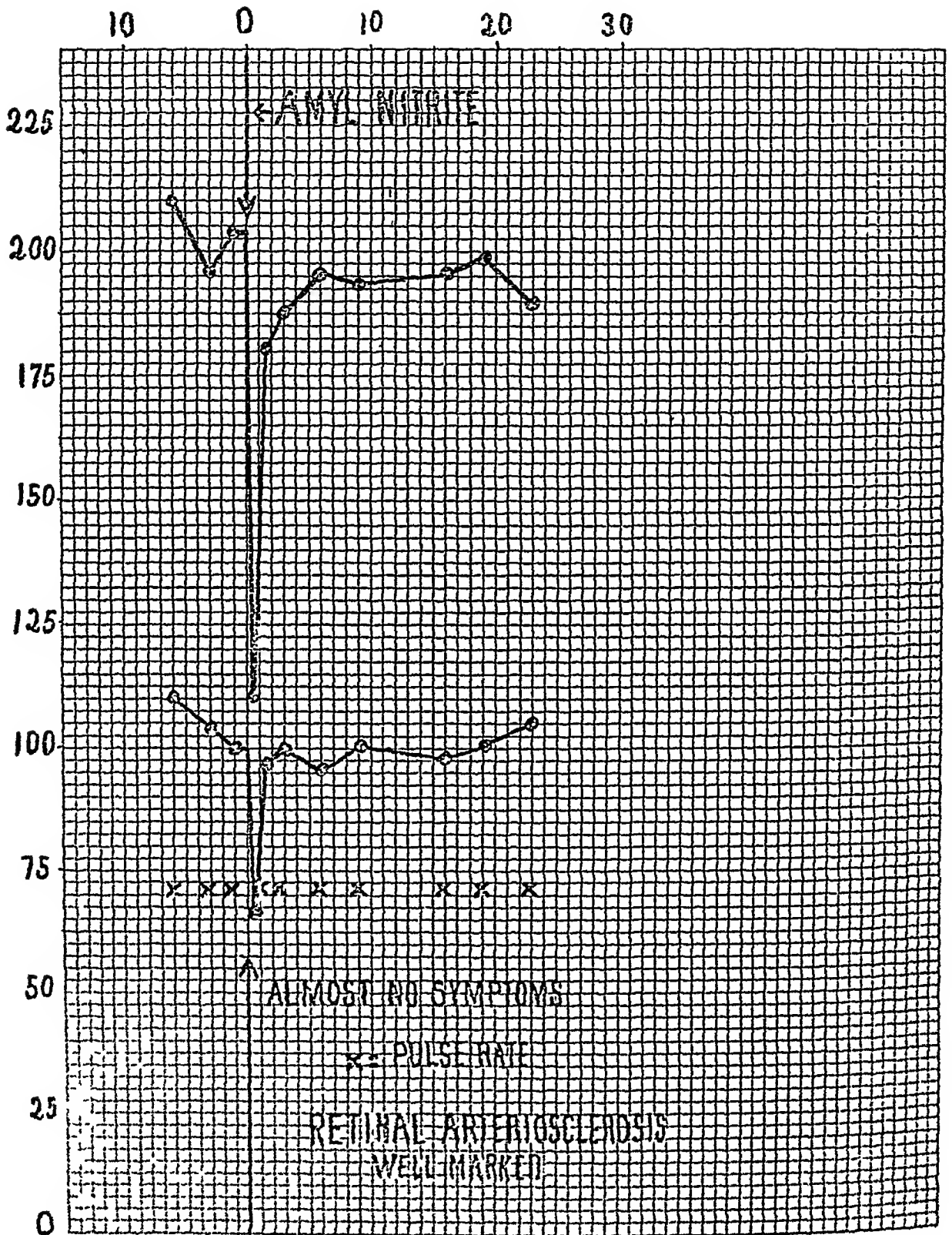


CHART 7 Arterial hypertension. Note marked response to amyl nitrite in spite of presence of tachycardia and other symptoms and in the presence of marked retinal arteriosclerosis

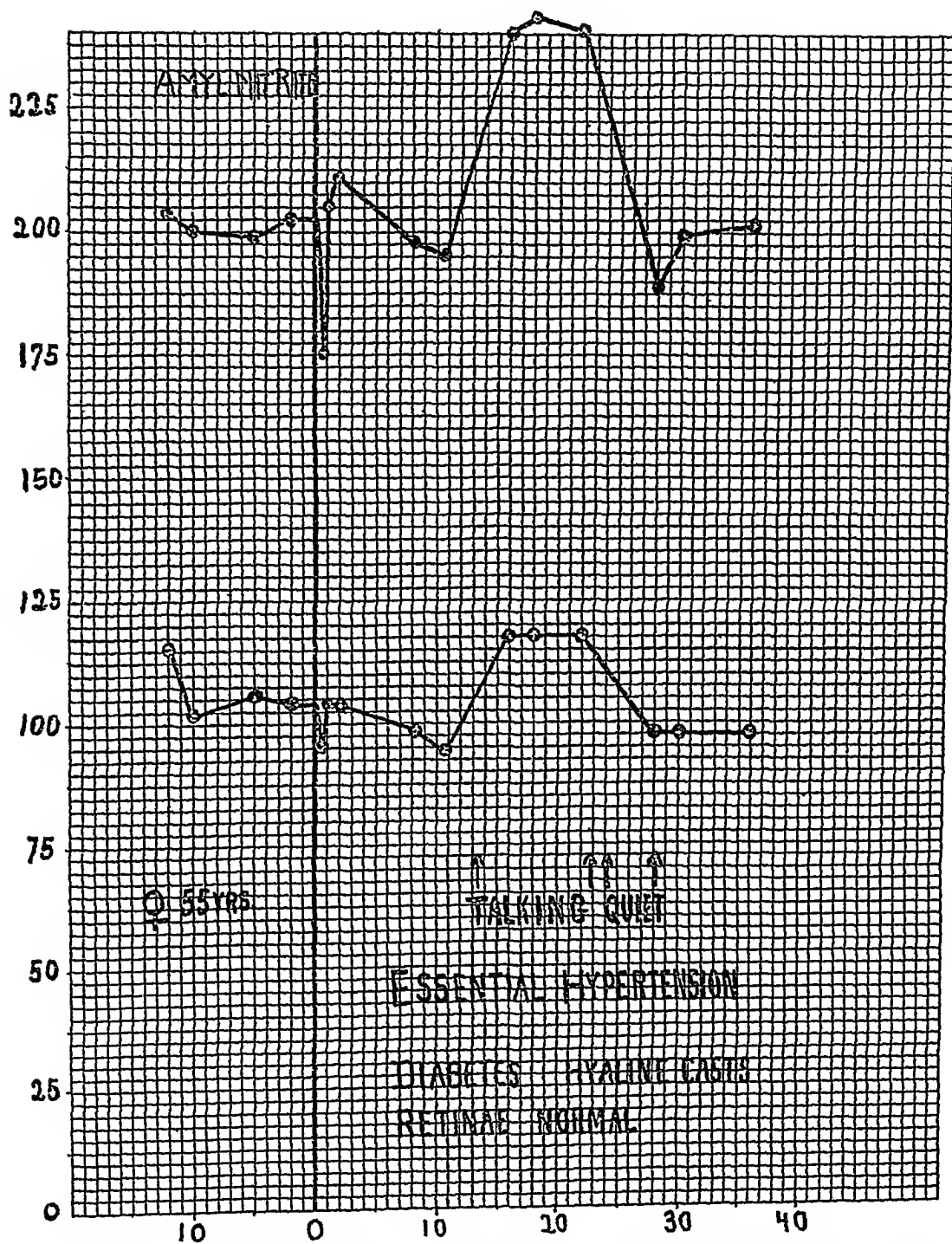


CHART 8 Arterial hypertension Note effect of animated conversation on blood pressure

any drop in diastolic pressure had been noted, and was well established before any effect more than a five mm drop had been observed even on the systolic pressure (See Charts 10, 11 and 12) In one instance complete relief had occurred when both systolic and diastolic pressures were within 5 mm of the point at which they were first observed (Chart 10) and in another (Chart 14) no drop whatever but an actual rise in diastolic pressure took place although there was at the time complete relief of the pain (The shaded areas on the charts which are intended to indicate the degree of pain are based on the patient's answers to repeated questioning during the tests)

(2) In the three attacks that were studied by the use of amyl nitrite the usual abrupt fall in 30 seconds followed by a quick rise in a minute and a half was found In two instances the pressure remained for the next twenty minutes at a distinctly lower figure than before the administration of the drug.

Relief of Pain. In no instance did the relief of pain correspond to the low pressure reading. One patient in whom, as is shown in Charts 11 and 13, the pressure had fallen abruptly, a drop of 70 mm systolic and 30 diastolic, stated that the pain had not changed in the slightest Three seconds later sudden relief took place, as he said, "like pricking a toy balloon" On a second patient (see Chart 12) thirty seconds after amyl nitrite when a drop of 70 mm systolic and 32 mm diastolic had occurred, there had been no change at all in the intensity of the pain but at the end of

one minute, although the diastolic pressure had returned to its former level of 110 mm and the systolic had risen to 180 mm, or three-quarters of the way back to the starting point, the pain had markedly diminished and after two and a half minutes had completely disappeared although the pressure readings were at that time very nearly what they were before the inhalation of the drug

Comment It is evident from the above that the relief from pain experienced after nitrite therapy in angina pectoris is independent of the decrease in systemic blood pressure—diastolic or systolic This certainly suggests that such relief is probably not due to nitrite dilation of the peripheral vessels The only other known action of nitrites which could relieve the pain, then, is the action on the coronary arteries—and if increased flow through the coronaries is the mechanism of the relief, the cause of the pain must be an ischemia of the heart muscle It is probable, then, that anything which causes an increase in the work of the heart such as excitement or exertion, with the known increase in peripheral blood pressure and heart rate which accompany them, causes in these patients a temporary ischemia of heart muscle The underlying cause of the whole picture must therefore be deficient coronary circulation which is incapable of supplying the physiologic needs of the musculature of the heart during periods of stress.

In connection with the reaction of patients with angina pectoris to nitrite therapy brief reference will be made to one patient, a lady of 76 years of

Two Attacks of Angina Pectoris

OFFICE

FD-350

GR 500

1-ADYCE RINE GRP

early crime

Director

Pain

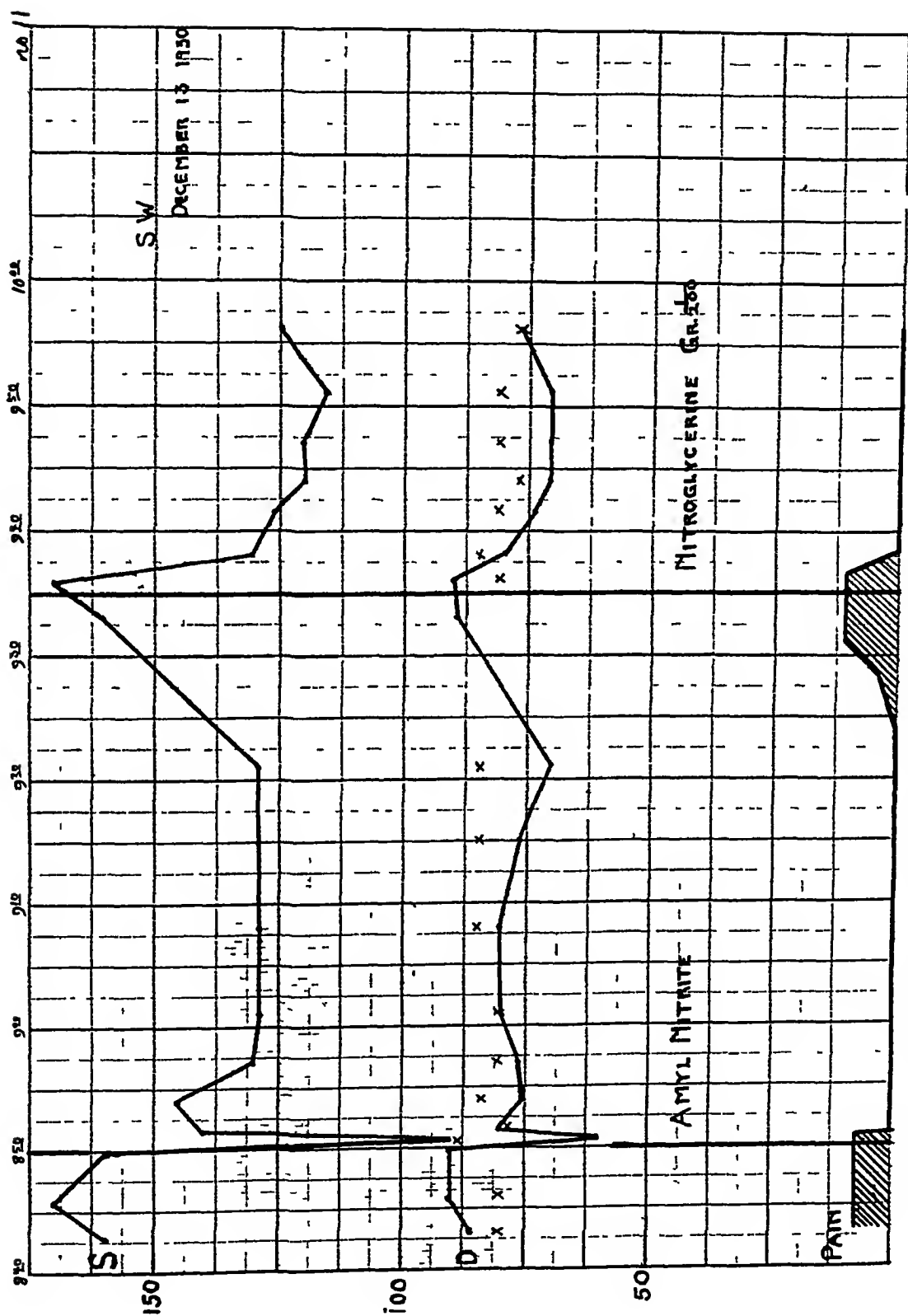


CHART 11 *Angina pectoris* Response of the same individual to amyl nitrite and nitroglycerine in two attacks occurring within an hour

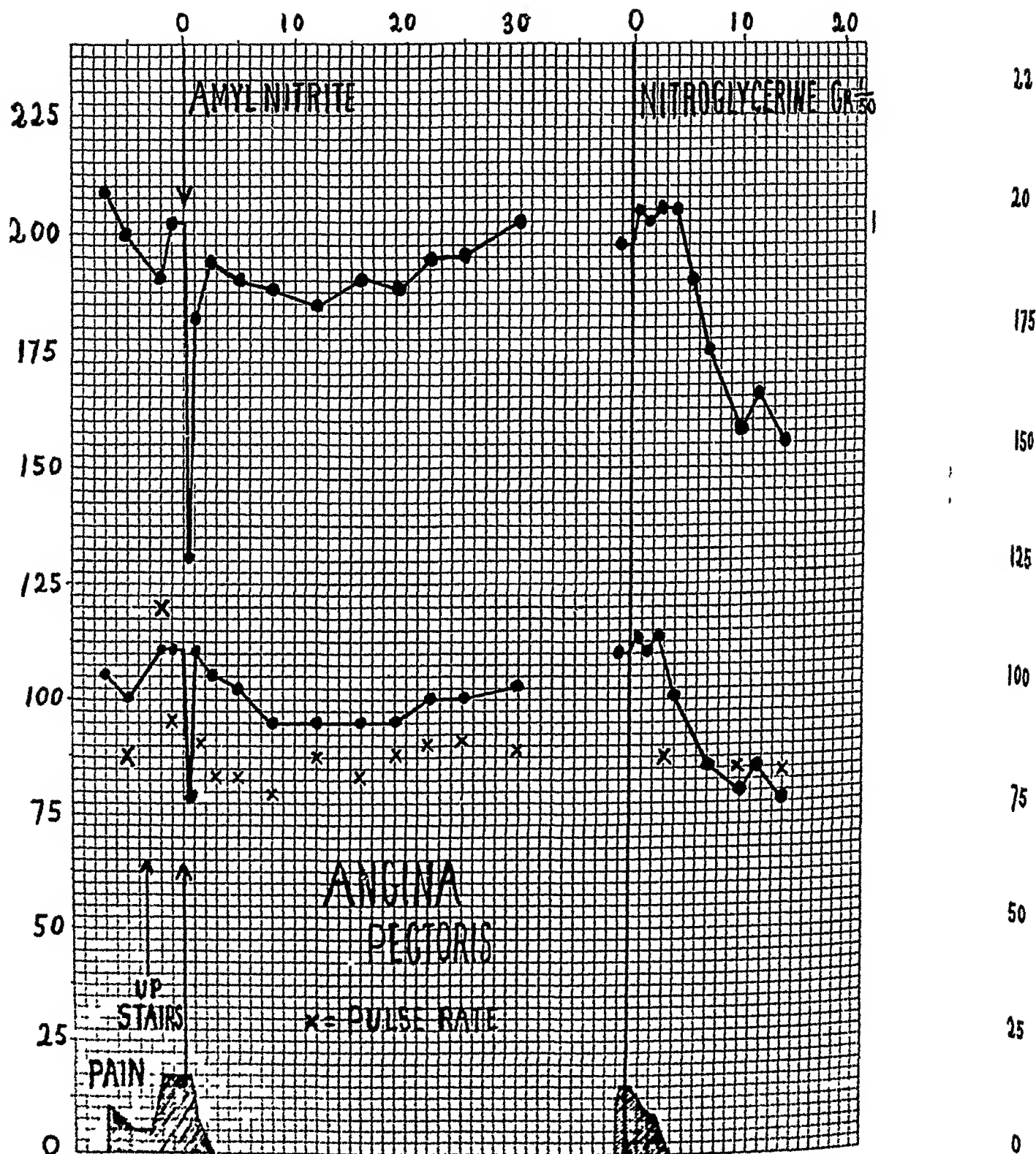


Chart 12 Angina pectoris. Response to amyl nitrite and nitroglycerine. Note but no correspondence between pressure levels and pain relief.

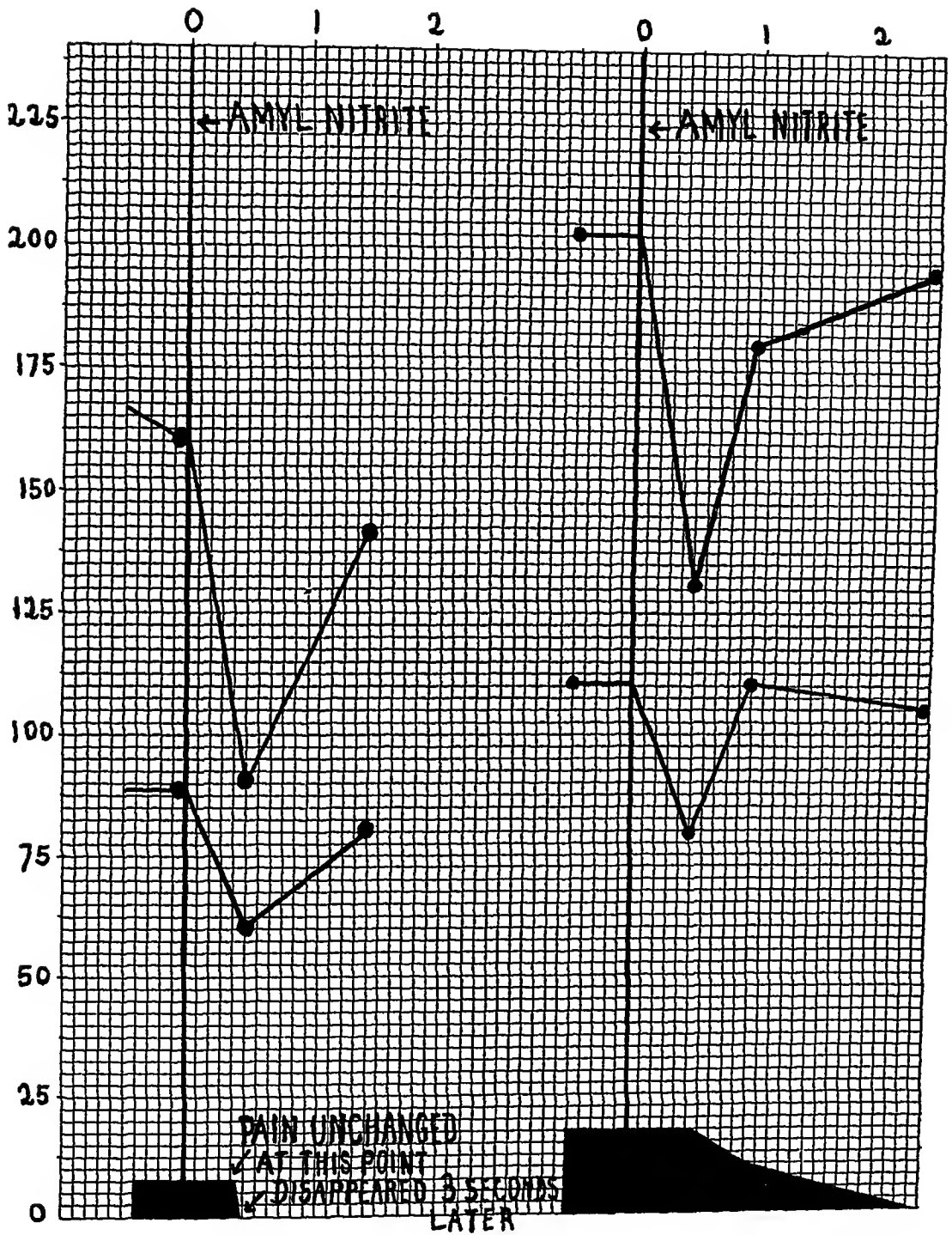


CHART 13 Angina pectoris Chart of pressure curves and pain relief in cases illustrated in Charts 11 and 12 drawn to a different scale to show more clearly the lack of correlation between fall in pressure and pain relief

age, in whom the administration of nitroglycerine gr 1/100 per os because of anginal pain of moderate severity, was followed, after the usual relief had been experienced, by a recurrence of much more severe and viselike pain, sweating, pallor and a further marked fall in blood pressure (Chart 16). All our clinical observations including electrocardiographic studies before and after the attack, confirmed the impression that while under observation the patient had suffered an occlusion of a branch of a coronary artery. This case will be reported later in detail. One certainly is led to suspect that in this instance the action of the nitroglycerine may have been a factor in bringing on or hastening the thrombosis of the coronary artery involved.

SUMMARY

Studies of the rapidly acting nitrites, nitroglycerine and amyl nitrite, in the usual therapeutic doses, on normal people, persons suffering from arterial hypertension and from the anginal syndrome showed the following results:

1. The usual symptoms, tachycardia, flushing, headache, etc., varied greatly and appeared quite independent of pressure levels.

2. Normal human beings after the application of nitroglycerine by mouth or hypodermically showed no consistent change in diastolic pressure. The systolic pressure also underwent no consistent change although there was in some instances a slight tendency downward.

3. The reaction of normal human beings to amyl nitrite was a sharp fall

in thirty seconds followed by a quick rise to above the previous level in about two minutes. Later blood pressure readings approximated the initial figures.

4. Patients with arterial hypertension with and without severe renal damage showed similar reactions. After nitroglycerine there were no consistent changes in either systolic or diastolic pressures. After amyl nitrite they showed a sharp drop in systolic pressure similar to that seen in the normal in the first half minute followed by a compensatory rise at times exceeding the former level. The diastolic pressure in some instances underwent a similar but less marked variation and in others almost none. Although the presence of a marked diastolic drop may indicate an early stage of arteriolar disease, as suggested by Stieglitz, it did not bear any definite relation to the presence or absence of sclerosis of the retinal arterioles in the patients studied. The rapidity of the drop and the compensatory rise made an accurate determination of the extent of the drop impossible.

5. In the presence of the anginal syndrome nitroglycerine caused a marked drop in systolic pressure within two to five minutes at times preceded by a slight rise in the first minute. The diastolic pressure usually but not always showed a fall also. After amyl nitrite the usual sharp fall in systolic and diastolic pressure occurred followed quickly by the compensatory rise. In both instances pain relief occurred promptly but was quite independent of pressure levels.

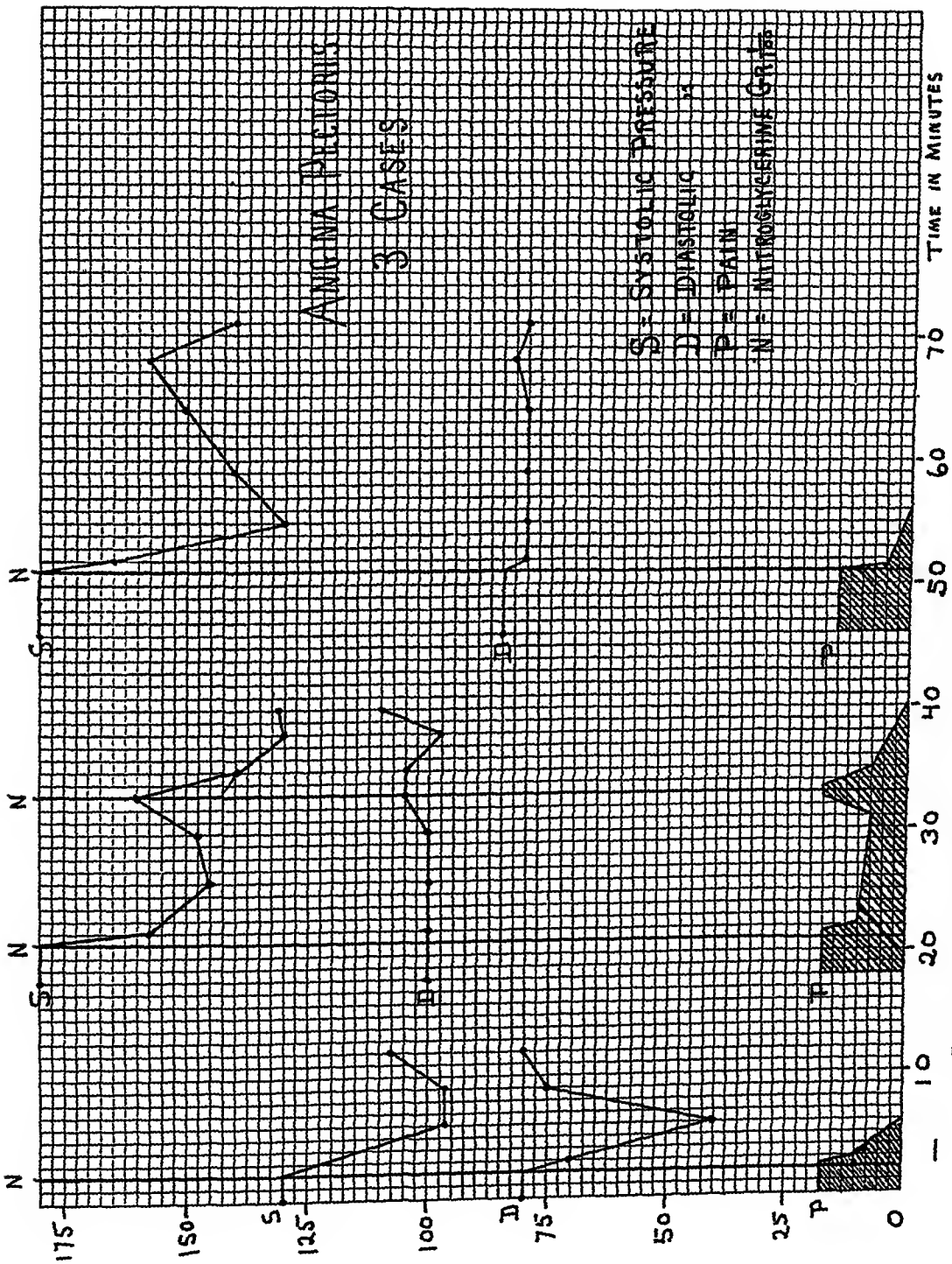


CHART 14 Angina pectoris Response of three different individuals in attacks Note absence of fall in diastolic pressure in second case in spite of complete pain relief

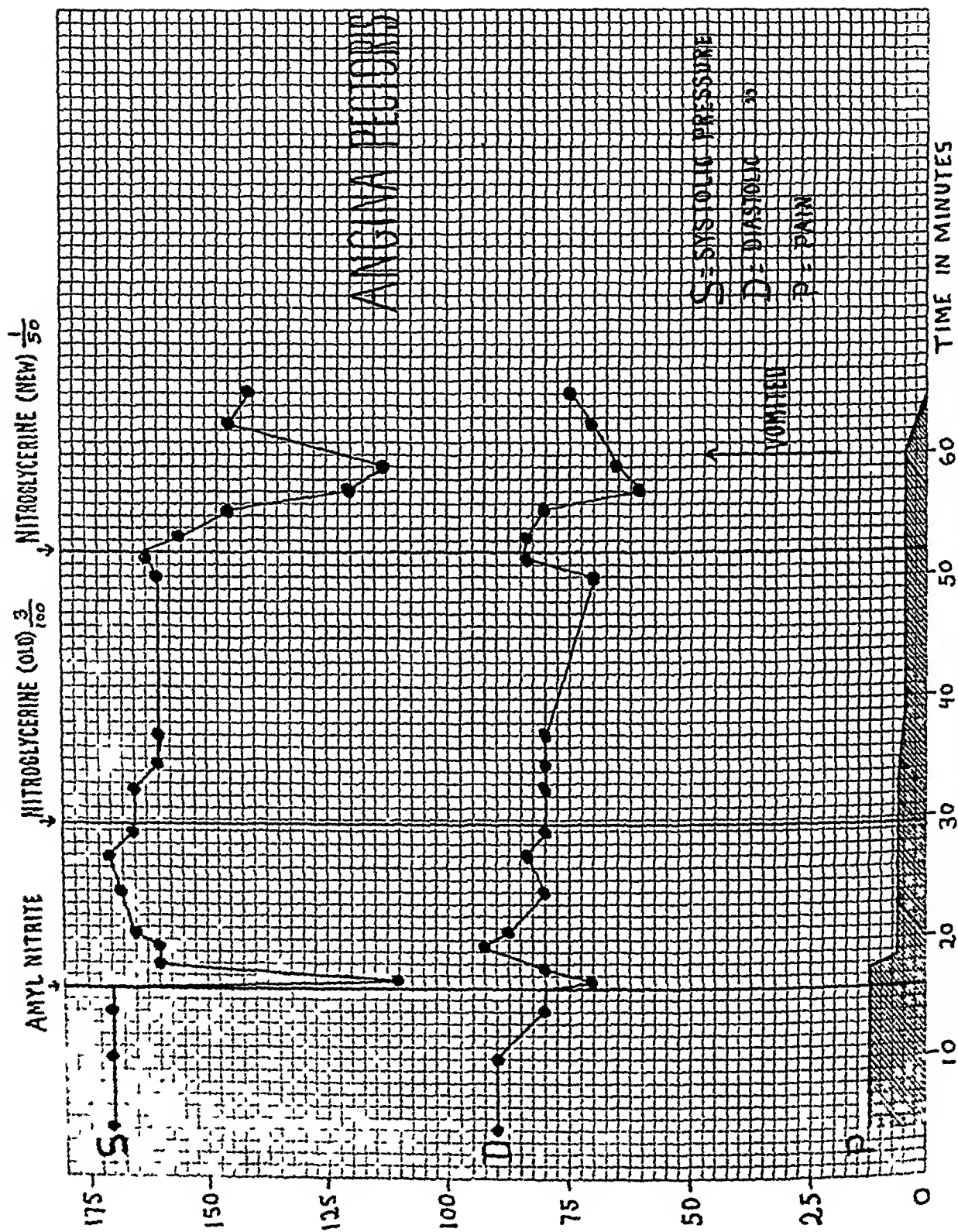


Chart 15. Angina pectoris—woman 76 years old who had previously had coronary occlusion illustrated in Chart 16. Note decrease of response to tablets of nitroglycerine when kept in the house about 4 months (marked nitroglycerine 'old' on chart).

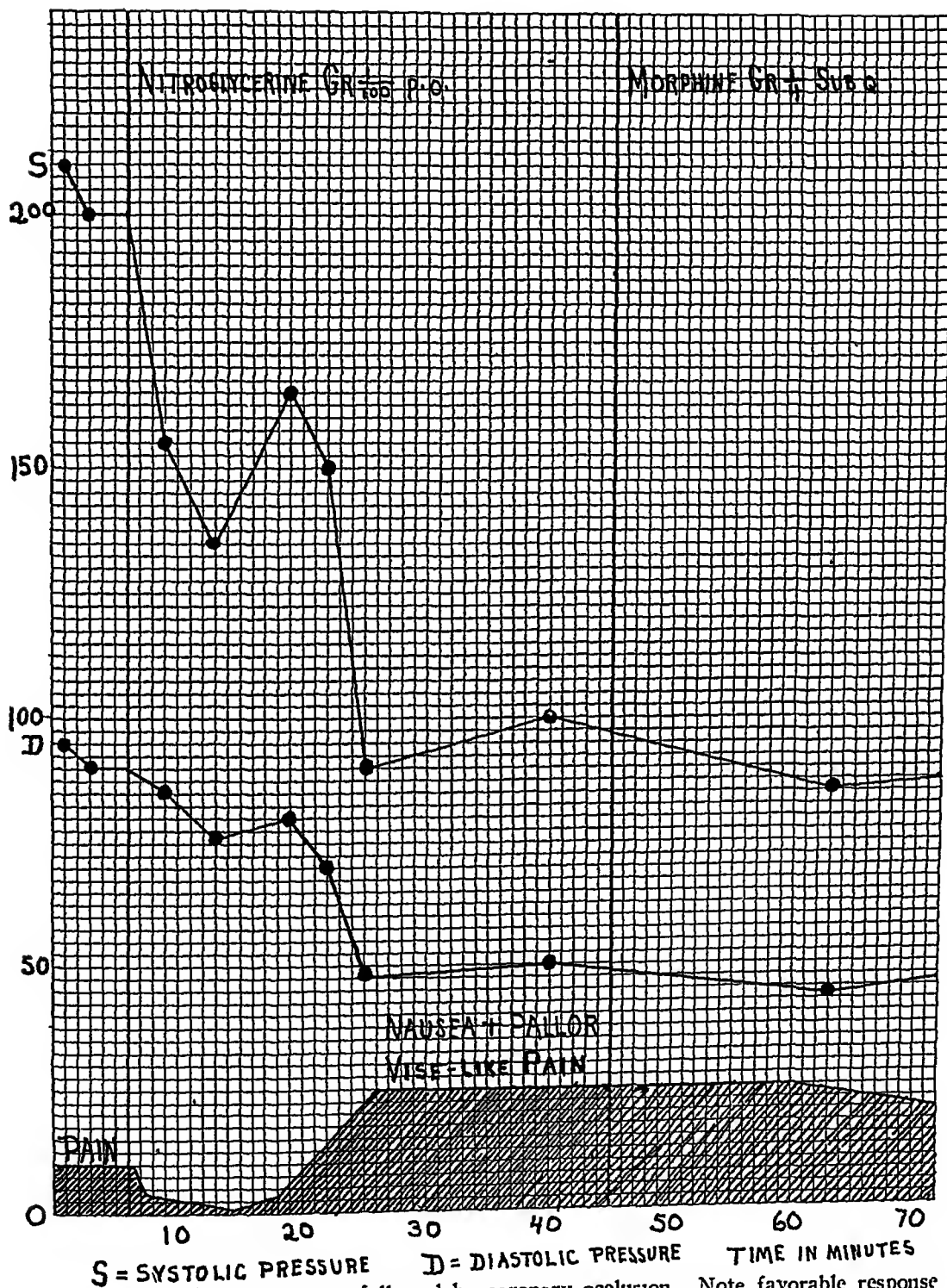


CHART 16 Angina pectoris followed by coronary occlusion. Note favorable response to nitroglycerine followed by return of severe viselike pain and a much more marked and permanent fall in blood pressure.

CONCLUSIONS

1 Except for a very transient fall in blood pressure after amyl nitrite, neither it nor nitroglycerine, when used in the usual therapeutic doses, causes any consistent blood pressure changes in normal human beings or in persons with arterial hypertension with or without severe renal damage or retinal arteriolar sclerosis.

2 The fall occurring after the use of amyl nitrite is so rapid and transitory and so independent of subjective symptoms, that it is impossible to measure it accurately by taking blood pressure determinations in the ordinary way. This fact greatly decreases its usefulness as a test for arteriolar relaxability in estimating the prognosis in arterial hypertension.

3. In persons suffering from attacks of angina pectoris of the usual ambulatory type, a rapid fall in systolic and usually in diastolic pressure takes place after the use of these drugs.

4. The pain relief which occurs in these cases of ambulatory angina is independent of the pressure levels and therefore apparently independent of the action of the nitrites on the peripheral vessels but due to their action in increasing coronary circulation.

5. The cause of the pain in ambulatory angina is probably an ischemia of the myocardium dependent upon an insufficient blood supply due to disease of the coronary arteries.

REFERENCES

- ¹STRICKITZ, E. J. Arterial hypertension: evaluation of the prognosis, *Arch Int Med*, 1930, xli, 227.
- ²WATLACE and RINGIER. The lowering of blood pressure by the nitrite group, *Jr Am Med Assoc*, 1909, lxi, 1629.
- ³STREIGHT, E. J. Loc cit.
- ⁴LIANKI, C. D., LOVINIART, A. S., and MITCHELL. Dilation of cerebral vessels as a factor in headache, *Jr Am Med Assoc*, 1927, lxxviii, 1076.
- ⁵RAPHANI, T., and STANTON, J. M. Action of certain drugs on brain circulation in man. *Arch Neurol and Psych*, 1910, ii, 389.
- ⁶MACHY, D. I. Action of nitrites on the isolated surviving pulmonary artery, *Jr Am Med Assoc*, 1914, lxi, 525.
- ⁷VOGELIN, C., and MACHY, D. I. *Jr Pharm and Exper Therap*, 1913, v, 77.
- ⁸SCHLOSS, KARL. *Deutsch Arch f Klin Med*, 1913, cxi, 310.
- ⁹LOEB, O. *Arch f exp Path u Pharm*, 1903, li, 64.
- ¹⁰SMITH, F. M. The action of the nitrites on the coronary circulation, *Arch Int Med*, 1921, xxxiii, 836.
- ¹¹KEHLER, C. S., and RISNIK, W. H. Angina pectoris: a syndrome caused by anoxemia of the myocardium, *Arch Int Med*, 1928, xli, 769.
- ¹²MAY, H. Die "Arbeits-reaktion" des Blutdruckes bei Gesunden und Kreislaufkranken und ihr Zusammenhang mit der Angina Pectoris, *Med Klin*, 1928, xxiv, 1704.
- ¹³LYMAN, D. Normal blood pressure in essential hypertension. *Jr Am Med Assoc*, 1930, xciv, 1214.
- ¹⁴BROOKS, H. Concerning certain phases of angina pectoris, *Internat. Clinica*, 1928, iv, 12-32.

Auricular Flutter and Complete Heart Block: With Restoration of Sinus Rhythm and A-V Conduction*

By LESLIE T. GAGER, M.D., *Clinical Professor of Medicine, George Washington University, Washington, D. C.*

NEITHER auricular flutter nor complete heart block are by themselves extraordinarily uncommon and it is safe to say that they would be even more familiar were the presumptive signs and symptoms of each borne in mind and the means taken for definitive diagnosis. The co-existence of these two disorders of the heart beat, however, is a clinical rarity. Previous to the example which is here reported, I find in the literature a total of fifteen cases of auricular flutter occurring in the presence of total auriculo-ventricular block, while in two patients only, those of Schott⁹ and of Gallemmaerts,¹¹ was there the joint restoration, under treatment, of sinus control and A-V conduction.

CASE REPORT

N. R., a negro laborer aged 70 years, worked until the day before his admission to the George Washington University Medical Service, Gallinger Municipal Hospital, on Jan. 20. His complaints were increasing shortness of breath and swelling of the ankles.

The family history was irrelevant and the patient had never been seriously ill. Vene-

real infection was denied and he had been moderate in the use of alcohol and tobacco.

His present illness began three weeks before admission with chills and fever and a dry cough, followed by dyspnea on effort, occasional palpitation and slight edema. He was able to sleep comfortably, his appetite and digestion were good, the bowels were regular and there was total absence of pain, fainting or convulsions.

The physical examination showed a well-developed, sparsely nourished old man lying flat in bed. Respirations were 16, regular and quiet. The jugular veins were not distended.

The pupils were active and the knee jerks present.

The retinal vessels were found without notable changes, the peripheral arteries were markedly sclerotic.

The apex of the heart gave its impulse in the sixth interspace 10 cm. to the left of the midsternal line. Apex and pulse rates were 44 per minute, the rhythm was regular. The blood pressure was 122/78. Clear heart sounds coincided with the apex rate, no intervening sounds were made out. The chest was full and the lungs were moderately emphysematous. There were numerous râles at the bases.

The liver edge was at the costal margin, not tender and the wall of the abdomen was relaxed.

Pitting of the ankles was present.

*Case presentation at clinic for the American College of Physicians, George Washington University Hospital, March 28, 1931.

The urine showed a specific gravity of 1.022, a faint trace of albumin and an occasional hyaline cast. Hemoglobin was 70 per cent, white blood cells 7,000, with poly-

morphonuclears 53, band forms 12, large mononuclears 5, and lymphocytes 30 per cent. There was a one plus Wassermann reaction of the blood.

A teleroentgenogram gave an aortic diameter of 7.4 cm, and the transverse cardiac diameter 16.1, with a thoracic width of 30.0 cm.

The electrocardiogram (figure 1) confirmed the clinical diagnosis of complete heart block, with a ventricular rate of 44

auricular or ventricular rate and was resumed from Feb 9 to Feb 16, at 60 minims (4 cc) per day, also without effect.

Quinidine sulphate was prescribed on Feb 16, in doses of 0.4 gm (gr vi) given three times daily.

On the first day of its administration, there occurred what the patient described as a "shaking spell all over" which lasted three hours and was without fever. Sub-

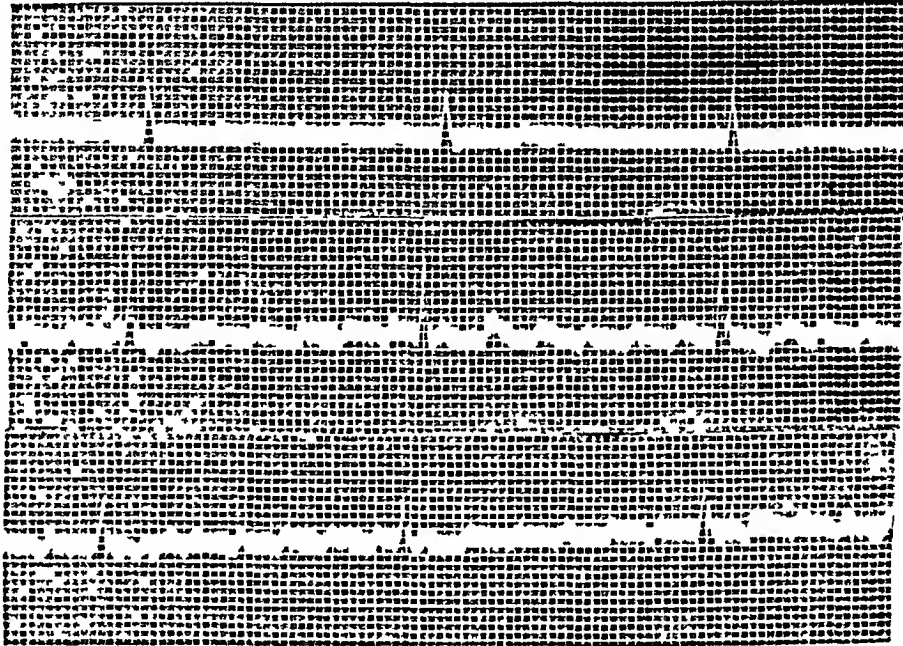


FIG. 1. Auricular flutter, rate 274, complete heart block, ventricular rate 44. Supraventricular type of QRS indicates origin in bundle. (Electrocardiograms by G. Edward Smith.)

beats per minute, and in addition it disclosed the presence of auricular flutter at 274 beats per minute.

The course of the patient was afebrile, the apex and pulse rates ranged from 42 to 52 per minute and respiration from 16 to 20.

Treatment at the outset in the presence of congestive heart failure, consisted in rest in bed. This was supplemented by full doses of digitalis, and in the 12 days from Jan 21 to Feb 2 the patient received 250 minims (62 cc) of standardized tincture without apparent effect either on the flutter or on the block. The flutter varied from 280 beats to 250 beats per minute. Between Feb 2 the digitalis was discontinued for a week without change in

sequently, the pulse and apex rates were found from 60 to 70 beats per minute, with a dominant regularity frequently broken by beats which were interpreted as premature. The electrocardiogram taken on Feb 24 (figure 2) shows the persistence of this arrhythmia and its nature. There has been a return to normal sinus rhythm, most clearly seen in Lead III. Lead II shows a period of auricular silence—sino-auricular block²—followed by ventricular escape.

As quinidine was continued the ventricular rhythm became entirely normal and on March 15 the drug was discontinued. On March 21, the electrocardiogram (figure 3) reveals normal sinus rhythm and its control of the ventricles. The same procedure

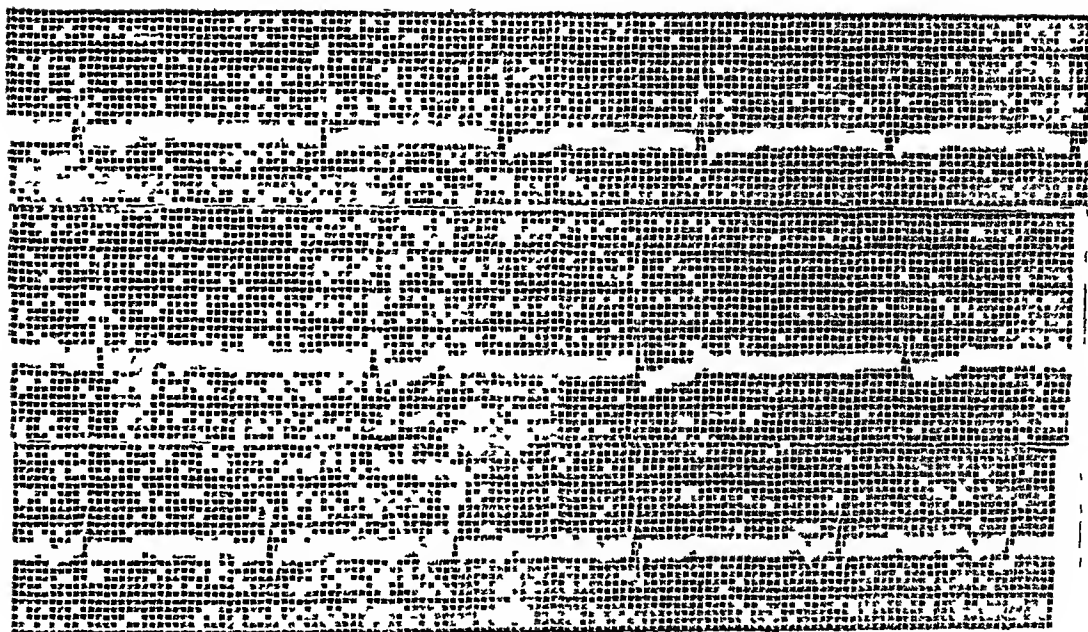


FIG 2 The response to quinidine Lead III best shows normal sinus rhythm and control of the ventricles P-R interval is 0.24 sec Lead II shows a transitory phase with auricular silence and ventricular escape The change in amplitude of the QRS waves is distinct

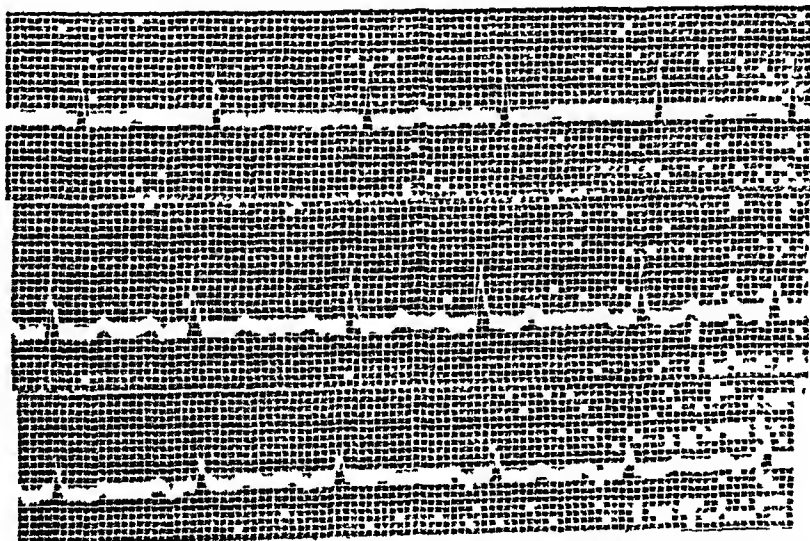


FIG 3 Complete restoration of sinus control, but persistence of delayed A-V conduction No quinidine has been given for one week and no digitalis for five weeks The QRS groups in II and III have decreased in amplitude and show notching

the P-R interval to 0.24 sec which was noted on Feb 24 is still present (For over a month, no digitalis has been given) The QRS complex occupies 0.08 sec, but is somewhat slurred and split The T wave is upright in all leads The rate in this record is 82

On March 25, an occasional prolonged pause and then a beat suggested the return of ventricular escape Quinidine was resumed, and upon discharge March 28, the rate was 72 to 76, the rhythm regular

The mental as well as the physical improvement of the patient under treatment is of interest It was noted at the time of admission that the patient was cooperative but his mind was dull and blurred and his responses sluggish He became ambulant after the first week, except during the first few days of quinidine therapy, but there is a note on Feb 25 that there is marked improvement in the mental condition along with the restoration of the normal heart rate

In summary, a man with arteriosclerotic heart disease, without cardiac hypertrophy or evidence of pre-existing hypertension, and without the history of Adams-Stokes attacks, suffering from congestive heart failure, showed complete heart block and by electrocardiographic demonstration, auricular flutter The auricular rate ranged from 260 to 280, the ventricular from 42 to 50, in the electrocardiograms Full doses of digitalis were ineffective but quinidine had a prompt action in abolishing flutter and restoring normal sinus control and heart rate A prolongation of A-V conduction time persists and there is further evidence of myocardial disease in the distortion of the QRS complex

REVIEW OF LITERATURE

It is noteworthy that clinical knowledge of auricular flutter begins with a patient whose complete heart block

furnished the incentive for further graphic study and then facilitated the analysis of the rapidly and regularly occurring "a" waves in the polygram

This patient of Ritchie's¹ was a man of 55. He came under observation with a pulse rate of 36 and a history of shortness of breath and attacks of faintness and giddiness since pneumonia six months before The blood Wassermann reaction also was positive After a period of normal auricular action, in June 1905, flutter at 274 beats per minute was discovered Observations were continued over a period of nine years^{2,3} At first paroxysmal or intermittent, the flutter became persistent in 1908 The ventricular rate ranged from 32 to 36, was occasionally elevated by premature beats and during one period showed groups of rapid beats (41 per minute) For two periods only, in 1913, did the auricular rate drop to normal, once after strophanthin and digitalis The Adams-Stokes attacks ceased after the establishment of flutter

In a woman aged 39 years, with rheumatic heart disease, Hertz and Goodhart,⁴ in 1909, found auricular flutter persisting for ten months at a rate from 216 to 230, with a ventricular rate as low as 44, though usually higher, from 72 to 120

A third patient was reported by Donzelot and Pezzi⁵ in 1914, a woman of 62 years, whose auricular and ventricular rates respectively were 360 and 35 to 40

Schott,⁶ in 1920, discussing ventricular standstill and the Adams-Stokes syndrome recorded these phenomena

in a woman aged 60 years who had had acute rheumatic infection six years before, and now showed runs of auricular flutter at 270 to 280 beats per minute and a ventricular rate sometimes in 4:1 ratio, during the course of which ventricular standstill was observed to occur, and sometimes independent ventricular rhythm at 58 beats per minute. Under digitalis the flutter merged into fibrillation and this into sinus rhythm, with recovery of excellent functional capacity. Repeatedly her life was saved, during the syncope of ventricular stoppage, by fist-blows over the heart.

Vinnis,⁷ in 1921, reported a man of 68, with hypertension of 285/125 and no symptoms except vertigo, with respective rates of 240 and 35 for auricle and ventricle.

Syphilis and the precocious arterial degeneration due to it were held responsible by Arillaga and Waldorp⁸ for the aortic insufficiency and complete heart block in a man of 42 years. The ventricular rate was 25 to 29, the auricular tachysystole 225 to 260. No improvement resulted from active anti-syphilitic treatment.

In 1922, Keating and Hajek⁹ witnessed the onset of flutter during her hospital stay in a woman aged 50 years who for four years had suffered from attacks of collapse and momentary unconsciousness. On admission, examination and electrocardiogram showed a simple tachycardia, rate 140. A week later, there occurred auricular flutter, rate 360 and complete block with ventricular rate 30. The auricular beats were audible. Later records showed a normal auricular rate, still later im-

pure flutter and fibrillation with many premature ventricular beats.

Wiltshire,¹⁰ in 1923, made particularly interesting observations in the case of a man of 63 years suffering from complete heart block, and periods of ventricular standstill lasting up to 67 seconds and occasioning severe Adams-Stokes attacks. During some of these periods of ventricular silence, auricular flutter was present, in others, sinus rhythm, in still others the auricles also were completely silent—in one record for 13 seconds during the attack and for four seconds after. It was observed that the auricular rate during one episode of ventricular standstill fell from 240 to 165, this slowing was considered evidence of exhaustion of the auricular muscle, presumably from lack of blood supply, for after the ventricles again began beating, the auricular rate rose at once to 214.

The patient of Gallemaerts¹¹ was a man of 62 years. There were attacks of asystole, the electrocardiogram disclosed ventricular bradycardia, complete A-V dissociation and auricular flutter. The use of quinidine caused reversion of the flutter to sinus rhythm, and made manifest a delay in conduction both in the main bundle and one of its branches. The syncopal attacks ceased.

Hall¹² found a history of bradycardia and fainting in a man of 62 years who sought treatment for intermittent claudication. The auricular rate was 270, ventricular rate 42. Right bundle branch block was present.

Willius,¹³ in 1927, described auricular flutter in a man of 50 with arteriosclerotic heart disease and congestive

failure Complete block had been established for five years The rates for auricle and ventricle were 236 and 36 Digitalis was not used in this patient, and quinidine had no effect This was the only example of the occurrence of auricular flutter with complete block in 108 cases of flutter discovered in the routine electrocardiography of 40,000 patients

Auricular flutter supervening in a woman of 50 years whose complete block had been observed for 11 years and whose history of slow pulse went back 20 years before this, was reported by Strauss¹⁴ The inciting cause of the flutter appeared to be a toxic adenoma of the thyroid Two months after thyroidectomy the rapid jugular pulse disappeared and the electrocardiogram confirmed the return of sinus rhythm The block persisted.

In the course of their large experience with flutter, Parkinson and Bedford¹⁵ encountered a man aged 74 years with congestive failure and slow pulse of two years duration The auricular rate was 270, the ventricular, 35 Under digitalis, the flutter was converted to fibrillation and two days later sinus rhythm was restored The complete block remained During flutter the auricular sounds were clearly audible at the apex, under sinus rhythm the auricular sounds were again heard but not so loud as with flutter

Henderson and Rennie¹⁶ reported auricular flutter with full heart block in a man aged 73 years who complained of weakness, fatigue and epigastric fullness The auricular rate was 201 and that of the ventricles 28 to 31 Atropine brought a slight in-

crease in ventricular rate but both conditions persisted and the patient died three months later

Finally, in 1930, Lian and Viau¹⁷ recorded their observations in a man of 54 years who came under treatment in 1927 for a complete block, with attacks of ventricular standstill and syncope, which disappeared under antisyphilitic measures In January, 1929, there were found complete heart block and right bundle branch block, auricular rate 84, ventricular rate 25 In April, 1929, the electrocardiogram showed flutter, at a rate of 242, ventricular rate 32 and left bundle branch block In May 29, following 25 mg of digitalin given over six days, the flutter disappeared, the complete dissociation remained, and the right bundle branch block reappeared

CRITERIA FOR DIAGNOSIS

When auricular flutter occurs singly, its presence is suggested by a regular persistent pulse of 120 to 170 beats per minute The diagnosis becomes reasonably certain if the pulse suddenly doubles in rate In other words, a 2:1 or 3:1 A-V ratio is suddenly converted to 1:1 rhythm But when transitions from one to another ratio are occurring frequently the pulse may not be regular, in the presence of the slower auricular flutter rates or of the higher auriculo-ventricular ratios, the rate of the ventricles may not excite attention For these and other reasons—such as the inconstant effect of vagus (carotid sinus?) pressure or of digitalization—recourse must be had to the electrocardiogram

As far as complete heart block alone is concerned, the idioventricular

rate is usually below 50 beats per minute and clinical diagnosis becomes the more assured as the rate falls to 40 and below. But total dissociation between auricle and ventricle is by no means stable; the ventricular rate, as in an aged physician under recent observation, may rise from 39 to 76 beats per minute, or the regular rhythm may be interrupted by ectopic ventricular beats or psychic influences and even changes in posture¹⁸ may produce the most striking changes in impulse conduction. In block, therefore, as in flutter, the evidence of the electrocardiogram is indispensable.

When, now, the two disorders of the heart beat are superimposed, the peripheral signs, such as apex and pulse rates, and the evidence of circulatory embarrassment, either transient in the form of Adams-Stokes attacks or in the more persistent congestive failure, are dominated by the block and ventricular insufficiency. Evidence of flutter must be sought in the way of abnormal auricular pulsations in the jugular veins or abnormal auricular sounds on auscultation either over the heart or over the jugular bulb. Fluoroscopy may disclose the auricular rate. But since these phenomena commonly are difficult, if not impossible, to elicit, once more the graphic methods must be looked to for an assured diagnosis.

PHYSIOLOGICAL CONSIDERATIONS

Without entering upon any extended discussion of the functions of heart muscle, particularly the properties of irritability, conductivity and rhythmicity which are especially concerned in the physiology of flutter and complete

block, it is possible to divide these cases into two groups.

In the first group are those in which the A-V dissociation was established prior to the onset of auricular flutter. Here perhaps the two disorders may be regarded as coincident in the course of progressive myocardial structural change; a definite interrelationship is lacking.

On the other hand, if flutter precedes, the possible effects of the rapid auricular impulses upon the capacity of the bundle for conduction or of the ventricle for excitation are to be considered. In experimental heart block Erlanger showed how increased auricular rate brought increase in the degree of dissociation; recently Herrmann and Ashman¹⁹ have discussed the mechanisms that may underlie both the gradual and the acute onset of complete block as well as of bundle branch block.

Certainly in the case which is here reported, as in the patients of Gallemaerts and Schott, the restoration of normal sinus rhythm would seem to have removed the factor of fatigue of the main bundle and thereby to have influenced the return of A-V conduction. In Lian and Viau's case the influence of flutter on bundle branch block is of interest. Parkinson and Bedford ascribe the 2:1 and 4:1 ratios (persistent 3:1 ratios are exceptional) to defective conductivity in the presence of flutter, the functional nature of which is shown by normal conduction when sinus rhythm returns.

The bearing which these facts have on treatment is that they suggest the importance of attempting, either by

digitalis or by quinidine or both, to restore sinus rhythm with the possibility of influencing A-V conduction

SUMMARY

A patient with auricular flutter co-existent with complete heart block was restored to sinus rhythm and A-V conduction by the use of quinidine sulphate. Physical and mental improvement resulted

Fifteen cases have been found in the literature showing the association of auricular flutter and total block and the clinical phenomena and criteria for diagnosis are reviewed

From experimental and clinical observations in partial block and from the results in three cases of complete block, the value of restoring sinus control in cases of auricular flutter is shown.

REFERENCES

- ¹RITCHIE, W T Proc. Roy Soc Edinb, 1905, xxv, 1085
- ²JOLLY, W A, and RITCHIE, W T. Auricular flutter and fibrillation, Heart, 1910-11, ii, 177-221
- ³RITCHIE, W. T. Auricular flutter, 1914, W Green and Son, Edinb
- ⁴HERTZ, A. F, and GOODHART, G W The speed limit of the human heart, Quart Jr Med, 1909, ii, 213-219
- ⁵DONZELOT, E, and PEZZI, C Tachysystolie de l'oreillette avec dissociation atrio-ventriculaire complète, Bull mém Soc méd d hôp de Paris, 1914, xxxvii, 497-506
- ⁶SCHOTT, E Über Ventrikelstillstand (Adams-Stokes'sche Anfälle) nebst Bemerkungen über andersartige Arrhythmien passagerer Natur, Deutsch Arch f klin Med, 1920, cxxxi, 211-229
- ⁷VINIS, E W. G. Nederl Maandschr v. Geneesk, 1920, lx, 113
- ⁸ARRILLAGA, F C, and WALDORP, C P La taquisistolia auricular enei sindrom de Morgagni, Stokes-Adams, Rev Asoc méd argent, 1921, xxxiv, 96-102
- ⁹KEATING, J. H, and HAJEK, J. Auricular flutter, Am Jr. Med Sci, 1922, clxiv, 656-677.
- ¹⁰WILTSHIRE, H Heart block illustrating behavior of auricle during periods of prolonged ventricular silence, Heart, 1923, x, 201-221
- ¹¹GALLEMAERTS, V Tachysystolie auriculaire et bradycardie, (Soc clin hop Bruxelles, 1923) Arch d. mal. du coeur, 1924, xvii, 529, Abstract
- ¹²HALL, D. Auriculo-ventricular bundle branch block, Brit Med Jr, 1924, i, 778-779
- ¹³WILLIUS, F A Auricular flutter with established complete heart block, Am Heart Jr, 1927, ii, 449-452
- ¹⁴STRAUSS, A E Heart block, auricular flutter and adenoma of thyroid, Med Clin. North Am, 1927, xi, 487-497
- ¹⁵PARKINSON, J., and BEDFORD, D E Course and treatment of auricular flutter, Quart Jr. Med, 1927, xxi, 21-50
- ¹⁶HENDERSON, J, and RENNIE, J. K Case of auricular flutter with full heart block, Glasgow, Med Jr, 1927, cviii, 355-358.
- ¹⁷LIAN, C, and VIAU, C Auricular flutter et bradycardie par dissociation auriculo-ventriculaire complète, Arch d mal du coeur, 1930, xxiii, 514-517.
- ¹⁸GALLEMAERTS, V. Orthostatic auriculo-ventricular dissociation Arch d mal du coeur, 1923, xvi, 332-343
- ¹⁹HERRMANN, G, and ASHMAN, R. Partial bundle-branch block. theoretical consideration of transient normal intra-ventricular conduction in presence of apparently complete bundle-branch block, Am Heart Jr, 1931, vi, 375-403

Primary Aplastic Anemia; A Discussion and Report of Two Cases*†

By JAMES B. CAREY, M.D., F.A.C.P., and JOSEPH H. TAYLOR, M.D.,
Minneapolis, Minn

THERE are various toxic and chemical agents, which may so affect the bone marrow that it is incapable of forming blood elements, and a condition of profound anemia may therefore occur. Infectious diseases, which progress to severe stages of toxicity or septicemia; benzol, trinitrotoluene; arsenic, roentgen rays and radium emanations can all affect the hematopoietic system in such a manner as to produce the clinical picture of an aplastic anemia. In certain chronic blood disorders and malignancy, there often occurs an exhaustive aplasia of the blood-forming tissues.

Excluding all known etiologic factors, however, there remains the primary or idiopathic case. Ehrlich¹ first described such a clinical entity in 1888. Since his report other terminology has been suggested. Pappenheim² suggests "a-regenerative anemia" and later Schneider³ suggests "toxic paralytic anemia" or "toxic anhemopoietic anemia". However, since at autopsy these cases show a completely aplastic condition of the bone marrow, a hypo-

plasia so profound that not even the normal amount of blood elements is found, with little hint as to the possible cause, it would seem that Ehrlich's original term is the most applicable. Any other designation implies etiologic factors, and none has been known.

Aplastic anemia patients are usually young adults or individuals of early middle age, in fair state of nutrition, showing pallor of either grayish or yellowish tinge, with hemorrhages into skin and mucous membranes. There is usually stomatitis and glossitis, progressing often to an extreme phlegmonous induration or gangrenous slough, and a septic type of temperature which may be due to the mouth lesions, especially as they usually become secondarily infected.

Further study of the case should reveal these other positive data.

1 Extreme anemia (counts as low as 500,000 or less with hemoglobin often too low to read accurately). The anemia is of the hypochrome type with no evidence of blood regeneration.

2 Leukopenia which also may be very low (1,000) with a relative lymphocytosis.

3 Thrombocytopenia, platelets may be too few to count accurately, usually less than 75,000.

*From the Department of Medicine, The Nicollet Clinic. Read before the Minnesota Society of Internal Medicine, April 13, 1931.

†Received for publication, April 14, 1931.

Pathologically, there is found an extreme hypoplasia, or aplasia of the bone marrow. The marrow grossly is soft, yellow and almost completely replaced by fat. The microscope confirms this gross appearance of inactivity by revealing extreme hypoplasia or complete aplasia of cellular structures.

The outcome of all cases is fatal and no treatment up to the present time employed has been of the slightest avail.

Hirschfield³¹ gives a complete bibliography up to 1911.

Sheard,⁴ in his monograph on pernicious anemia and aplastic anemia, has covered the bibliography up to 1923 and discovered about 125 authentic cases. Since 1921 there have appeared in the literature reports,⁵⁻²⁴ presenting about twenty further adult cases. Schneider³ mentioned sixty cases found up to 1918. There are several discussions of primary aplastic anemia based upon an indeterminate number of cases²⁵⁻³³. Many of these cases and discussions are in inaccessible literature; those papers found dealing with various phases of the subject are sometimes indefinite as to the actual number of cases on which the discussions are based. It may be estimated with reasonable accuracy, however, that not over 150 cases of primary aplastic anemia so far have been reported. A few cases reported among children were rather obviously anemias of hemorrhagic and aplastic type, following directly as the result of severe infections, and must therefore be excluded when considering only idiopathic cases. Some of Sheard's mentioned reports are of this category. There are

many cases of pernicious anemia reported with so-called aplastic tendencies, meaning that there may be a stage in pernicious anemia when the bone marrow becomes aplastic, all blood elements consequently becoming reduced, hemorrhages occur and the patient dies.

The diagnosis of primary aplastic anemia is, in fact, often difficult and lies somewhere among several conditions; hemorrhagic and aplastic type of blood reactions occurring secondarily to sepsis, infection, sudden grave hemorrhage, pregnancy, poisons (benzol, trinitrotoluene, arsenic) and exposure to x-ray and radium. No difficulty is encountered if the primary agent can be determined. There are four diseases, however, which may cause confusion; thrombocytopenic purpura, pernicious anemia, aleukemic leukemia and agranulocytic angina. In leukemia, even in the aleukemic stage, there will probably be adenopathy and splenic enlargement and certain characteristic elements in the blood picture. The anemia will probably not be so profound, nor will the hemorrhagic features be so abundant or severe.

In pernicious anemia the history is usually of much longer duration and contains references to gastrointestinal symptoms, paresthesia and glossitis. There are evidences of hemolysis in skin, urine, duodenal contents, blood serum and feces. The anemia in pernicious anemia is not so profound until the end stages at least, nor are the hemorrhagic features prominent, although often present. In pernicious anemia there is also characteristically present an achlorhydria and usually evidence of subacute combined degener-

eration (posterolateral sclerosis) of the spinal cord. The platelet count is not likely to be so completely reduced, nor is there such a marked leukopenia. The anemia is of the hyperchrome type.

In thrombocytopenic purpura the hemorrhagic features are more marked, and the anemia and leukopenia less so than in aplastic anemia. The morphology of the blood elements is practically normal.

Agranulocytic angina is a condition in which a severe gangrenous stomatitis develops and is accompanied by a blood picture of complete or almost complete absence of granular (polymorphonuclear) leukocytes. The red blood cells and hemoglobin may remain within normal range. The patients are usually middle aged females, and the disease is rapidly fatal (within two weeks ordinarily). There is, on account of the relatively normal hemoglobin and red count, no pallor, and the hemorrhagic features are usually absent. Piney has mentioned the agranulocyte reaction as sometimes occurring in aplastic anemia, but none of the formally reported cases have shown such phenomena.

Pathologically, the differentiation is not difficult from an examination of the bone marrow alone⁸⁴. In aplastic anemia a soft, yellow, fatty hypoplastic or aplastic marrow is evident, in pernicious anemia the red marrow is increased, and shows hyperplasia. In thrombocytopenic purpura there is also a red, cellular marrow with an increase of blood elements and decrease of fat. The degree and kind of hyperplasia is not, however, that of pernicious anemia. In leukemia there is

found a preponderance of lymphatic elements in the marrow. Further post mortem studies show in pernicious anemia the cord sclerosis or in leukemia the various characteristic glandular and splenic overgrowths. The bone marrow in agranulocytic angina does not show any characteristic changes of red cell elements, but granular cells are absent.

Two cases of idiopathic aplastic anemia are herewith described, and commented upon.

Mr S S, a farmer aged 33 years, a resident of Minnesota, consulted one of us (J B C) on November 5, 1929, complaining of weakness and swelling of the abdomen. He said that in September, 1929, he first began to become easily fatigued while at his work. About this time he sustained a fall, bruising his left side, after which he noticed some abdominal swelling. His local physician told him he probably had some fluid in his abdomen. He became weaker from that time until consulting us, but did not lose weight. He had no gastro-intestinal symptoms other than a capricious and variable appetite and the feeling of distention. He had daily bowel movements, which retained a normal color and consistency. There were no urinary symptoms. His skin became pale and slightly yellow, but there was no itching. His tongue had occasionally been sore.

The only illness he had had in the past was an attack of pleurisy in 1924. His family history was negative.

Physical examination on November 5th showed a pale man, rather dyspneic on slight exertion, with abdominal distention. He was fairly well nourished, but of poor muscular tone. The skin and mucous membranes were very pale, and slightly yellow, but not jaundiced. The hair had begun to turn gray. The tongue was moderately atrophic, with a whitish area on the right side, the site of recent glossitis. The heart was normal, except for a systolic "hemic" murmur heard at the base. The lungs were clear. The abdomen was tympanitic, mod-

erately distended, but revealed no masses or other abnormalities. The liver was barely palpable at the right costal margin and seemed of normal consistency. The spleen was palpated with difficulty on account of the distention and was slightly tender. The reflexes were present and normal, and vibration sense over the inner malleoli as estimated by the "C" tuning fork was normal. There was slight edema of both ankles, extending one-third of the distance up the tibiae.

Gastric secretory analysis showed a complete absence of free hydrochloric acid with a total acidity of 27. Fluoroscopic examination of the stomach, after ingestion of a barium meal, showed a large atonic organ without defects. The barium filled bowel, by fluoroscope, was likewise atonic and contained much gas, but was otherwise negative. The urine was light amber in color, 1017 specific gravity and acid in reaction, with 2+ albumen, but no sugar. A few blood cells and an occasional hyaline cast were seen. There was a trace of urobilinogen and no urobilin. The blood serum bile index was 8 to 9. Blood Wassermann and Kahn reactions were negative. Blood pressure was 110/80. There was no lymphatic glandular enlargement. An examination of the blood showed coagulation time 4'15", bleeding time 12', and 50,000 platelet count. Hemoglobin was less than 10 per cent and the red blood cells numbered 500,000. There were 1,250 white blood cells with 64 per cent of polymorphonuclears, 23.5 per cent lymphocytes, 12 per cent monocytes and 0.5 per cent eosinophils. The polymorphonuclear elements showed a distinct shift to the left, with several young and immature forms. There were none of the so-called pernicious anemia neutrophils present. The smears of the red blood cells showed a distinctly aplastic tendency, with more anisocytosis and poikilocytosis than normal and only an occasional hyperchromatic or polychromatic cell; there was, however, no achromia. There was also an occasional nucleated red cell seen.

The patient was placed in the hospital and grouped for transfusion. He was found to be a Group IV with, however, rather atypical agglutination reactions to Group IV sera. A transfusion of 375 cc of citrated blood was given on November 6th. There was a moderate reaction about two hours following the transfusion, controlled by 10 m adrenalin given by hypodermic injection subcutaneously. Liver extract (Lilly 343), 6 vials daily in orange juice, was begun and the patient placed upon the "Minot-Murphy" liver-containing diet.

The patient was given two other transfusions on the 9th and 17th, each followed by a very severe reaction, and neither of these additions of blood had appreciable effect upon the blood count, as even from the records below. A glossitis developed which became very severe, and spread onto the under surface of the tongue and to the buccal membrane. This lesion was undoubtedly responsible for the slight elevation of temperature noted constantly (100° to 101°, and at the time of transfusion reaction, 104° to 106°). Bleeding from the gums and rectum subsequently occurred; 50 cc of whole blood was used intramuscularly on two occasions, November 15th and 18th, in an unsuccessful attempt to control these hemorrhages. Petechial and purpuric spots appeared in scattered places over the body, and finally a day before death the surface of the abdomen was almost solidly covered with subcutaneous hemorrhages. The appetite remained good until the last two days, and the six vials of liver extract were continued until the last day. Death occurred November 27th, after a period of unconsciousness with elevated pulse (120), temperature (104°) and Cheyne-Stokes' respiration. An autopsy request was refused.

A few of the blood counts are herewith given (those showing transient effect of transfusion and whole blood injections are eliminated).

Nov. 7	Hgb	20%	Rbc	950,000	
Nov. 11	Hgb	10%	Rbc	800,000	
Nov. 16	Hgb	12%	Rbc	580,000	— no reticulocytes
Nov. 23	Hgb	15%	Rbc	520,000	
Nov. 27	Hgb	10%	Rbc	450,000	Wbc 8,600, no reticulocytes.
					(This count was done just before death.)

COMMENT

The phlegmonous, almost gangrenous lesion of the tongue had been described in many of the other cases of aplastic anemia reported in the literature. The temperature also is a common finding in this type of anemia. Although the blood bile index was slightly elevated, there were no other very striking evidences of extreme blood destruction, such as are often seen in end stages or crises of true pernicious anemia. The bile pigments of the urine were normal, the stool was of normal color and neither skin nor sclera were at any time marked by jaundice.

The blood count was very low, and did not react to the stimulation of liver, liver extract, blood transfusions or whole blood injections. There was free bleeding from the gastro-intestinal tract and subcutaneous hemorrhage. There was an achlorhydria present, but no signs of combined cord sclerosis. There was an absolute leukopenia at the beginning. The terminal rise seen may have been the result of the transfusions and whole blood, or both. The history of the illness was of short duration and showed a rapid progression to the fatal termination.

The second case is that of a white male age 42 years. He presented himself to one of us (JHT) for examination on October 15, 1930, complaining of weakness, dyspnea and "anemia." About a month previous to this admission he had had a severe sore throat with fever, for which he remained in bed for two weeks. During this time he had palpitation, became weak, suffered dull headache and experienced occasional slight bleeding from the gums. These symptoms all continued and were still complained of when he consulted us. His family history was nega-

tive as to any anemia or other constitutional diseases. In the fall of 1929 he had had some epigastric distress and heartburn, for which he consulted a physician, who made a diagnosis of duodenal ulcer, and placed him upon diet and medical management. He obtained relief gradually from these symptoms, and had regained what he considered to be normal health at the time when he suffered the severe angina mentioned.

The original physical examination showed a fairly well nourished man of rather poor muscular tone. There was marked pallor of the skin and mucous membranes, but no jaundice. The pupils reacted to light and accommodation normally. The sclera were clear. There was moderate gingivitis at this time, but no stomatitis or glossitis. The tongue was not atrophic. The breath was foul, and there was hypertrophy of the tonsils with evidence of recent hemorrhage from the right one. The heart and lungs were normal. Neither the liver nor spleen were palpable. There were no masses, fluid or other abnormalities revealed by abdominal palpation. Deep reflexes and vibration sense were normal. Examination of the gastro-intestinal tract after ingestion of barium by fluoroscope was entirely negative. Urine examination revealed a specific gravity of 1013, acid reaction, no albumin or sugar, no bile or bile pigments. There were no casts, but an occasional red blood cell was recorded. Numerous stool examinations, made during his subsequent hospital sojourn, were negative for occult blood, parasites and ova. Blood Wassermann and Kahn reactions were negative. Gastric secretory analysis showed free hydrochloric acid 49, total acidity 69, blood bile index was 4 to 5. Examination of the blood resulted in the finding of a hemoglobin of 35 per cent (Dare), red blood cells 1,960,000, color index 0.92, white blood cells 2,100, polymorphonuclears 20 per cent, lymphocytes 75.5 per cent, monocytes 4.5 per cent. Bleeding time was 13 minutes and coagulation time 4 minutes, 45 seconds. The blood smears were essentially normal and remained so. The patient was hospitalized. The general hospital diet was ordered, and one ampule of Ventriculin was administered three times daily. The use of the Ventriculin was continued until the pa-

tient became too weak to eat or drink anything during the last two days of his life. During his stay in bed he gradually developed a stomatitis, which, as in the previous case, became very severe. Smears showed Vincent's organism and much secondary infection.

The patient was grouped and transfused twice, on Oct 27 and Nov 5. Following both transfusions, there were very severe reactions with chill and elevation of temperature. Just as in the previous case, these transfusions had no appreciable effect upon the blood counts, as seen by the following record: Oct 22, hemoglobin 46 per cent (Sahli), red blood cells 2,000,000, white blood cells 8,000, no reticulocytes. Oct 31, hemoglobin 47 per cent (Sahli), red blood cells 2,300,000, white blood cells 6,000. Nov 4, hemoglobin 42 per cent (Sahli), red blood cells 1,650,000, white blood cells 6,000, no reticulocytes. The increase in the leucocytes was undoubtedly due to the mouth infection, and perhaps also influenced by the transfusion and continuing hemorrhages.

Fibrogen was given in one and two cc doses subcutaneously on numerous occasions in the last few days in an attempt to stop the hemorrhages, and on Nov 6th 20 cc of whole blood was injected intramuscularly—all without effect on the bleeding.

During the seventeen days in the hospital, the temperature ranged from 98° to 104.8° F, the pulse from 76 to 116 and the respiration from 20 to 34. He suffered repeated, almost continuous, hemorrhages from the gums; was very uncomfortable on account of the stomatitis and finally after several large gastric hemorrhages, he died on Nov 7, 1930.

An autopsy was performed on the same day by Dr. N. M. Levine of the Department of Pathology of the Medical School of the University of Minnesota from whose complete and detailed report the following positive and pertinent findings are taken. There were diffuse ecchymoses over the trunk, and also scattered petechiae over

neck, chest and upper abdomen. There were also small petechial hemorrhages internally on the surface of the heart, pleural and peritoneal surfaces. The heart was otherwise normal and likewise the lungs, except for hypostatic congestion and edema of the latter. The liver was of a pale brownish red color. On opening the stomach, no ulcer was found, but submucous hemorrhages were numerous. The kidneys were normal, except for petechiae in the pelvis. The spleen weighed 175 gm, and was normal grossly and in cut section. The bone marrow of the upper part of the femur was uniformly yellow and fatty, that of the ribs was yellowish pink. The anatomic diagnosis was primary aplastic anemia with multiple hemorrhages. The bone marrow, in microscopic section, showed marked hypoplasia of all elements and likewise a marked decrease of leucocytes was especially noted.

COMMENT

This case proved to be a primary aplastic anemia by autopsy findings and showed essentially the same picture and clinical course as the first one detailed. In this second case, the onset was precipitated by an infection—a severe sore throat. The course was practically the same in both cases, progressive weakness, multiple and repeated skin and visceral hemorrhages, the development of severe stomatitis, gangrenous in the first and complicated by Vincent's infection in the second. There was no stimulation of blood regeneration in either case by use of liver, liver extract or hog stomach extract. Injection of whole blood had no effect on the tendency to hemorrhage or the thrombocytopenia in either case.

REFERENCES

HUBER, P. Ueber einen Fall von Anämie mit Bemerkungen über regenerative Veränderungen des Knochenmarks, *Chirurgia Ann.*, 1892, 100, 779.

PAPPELHIM, A. J. Pathologie, Symptomatologie und Therapie der Anämien und hämorrhagischen Diathesen, *Folia Haematologica*, 1912, 201 (2), 75.

- ³SCHNEIDER, J P Idiopathic aplastic anemia, *Am Jr Med Sc*, 1918, clvi, 799
- ⁴SHEARD, ARTHUR Pernicious anemia and aplastic anemia, 1924, Wm Wood & Co
- ⁵WILLIAMS, E C P Two cases of aplastic anemia, *Lancet*, 1921, ii, 74
- ⁶LEVI, E Case of aplastic anemia, *Gazz d'osp*, 1921, xlii, 487
- ⁷FONTAINE, B W. Aplastic anemia differential diagnosis of anemias due to hemolysis and due to hemopoietic degeneration, *South Med Jr*, 1923, xvi, 495
- ⁸DYKE, S C Some cases of aleukia or aplastic anemia associated with thrombopenia, *Lancet*, 1924, i, 1048
- ⁹FABERI, M Roentgen-ray treatment of aplastic anemia, *Policlinico*, 1924, xxxi, 1229
- ¹⁰FLEMING, R A, and DAVIDSON, J Aplastic anemia, *Trans Med-Chir Soc, Edinburgh*, 1923, xxxviii, 41-45 *Edinburgh Med Jr*, 1924, xxi, 41
- ¹¹FLEMING, R A, and DAVIDSON, J Case of myelogenous leukemia and case of aplastic anemia, *Brit Med Jr*, 1922, ii, 1074
- ¹²YOUNG, F W Aplastic anemia, *Ill Med Jr*, 1925, xlvii, 142
- ¹³DENECKE, G Remarkable case of aplastic anemia, *Deutsch Arch f klin Med*, 1926, cl, 266
- ¹⁴KINGSBURY, J G Primary aplastic anemia, *Guy's Hosp Rep*, 1926, lxxvi, 85
- ¹⁵CABOT, RICHARD Case 13101, An obscure anemia, *Bost Med and Surg Jr*, 1927, cxcvi, 404.
- ¹⁶STOTZIK, N, and GALPERIN, A Aplastic anemia, *Russk Klin*, 1927, vii, 716
- ¹⁷FOURNIER, J C M, GARRA, A, ROCCA, F, and MONESTIER, J Case of aplastic anemia, *Bull et Mem Soc méd d'hôsp de Paris*, 1928, lii, 190
- ¹⁸VAN PAASSEN, P Case of aplastic anemia, *Nederl Tijdschr v Geneesk*, 1928, ii, 3378
- ¹⁹VAN PAASSEN, P Aplastic anemia, six cases, *Nederl Tijdschr v Geneesk*, 1928, i, 2164
- ²⁰LOMBARD, P Anémie aplastique, *Arch Med Belges*, 1923, lxxxi, 331
- ²¹CONNER, H M Acute aplastic anemia, report of case, *Proc Staff Mayo Clinic*, 1928, iii, 139
- ²²McGOWAN, J P Further contribution to subject of aplastic anemia, *Proc Roy Soc Med*, 1928, xxi, 33
- ²³SABRAZES, J, MICHELEAU, P, and MANDILLON, G Myélose globale aplastique avec monocytose, anémie grave progressive avec leucopenie, thrombopenie, diminution du nombre des grands monocytes, modifications profondes de la moelle osseuse sternale prélevée "intra vitam," *Arch d mal de coeur*, 1928, xxi, 656
- ²⁴EDIE, E B Primary aplastic anemia, liver treatment without effect, *Penn Med Jr*, 1929, xxxii, 50
- ²⁵DUKE, W W Aplastic anemia, *Jr Am Med Assoc*, 1928, xci, 720
- ²⁶DUKE, W W The pathogenesis of purpura hemorrhagica with especial reference to the part played by blood platelets, *Arch Int Med*, 1912, x, 445
- ²⁷DUKE, W W The relation of blood platelets to hemorrhagic disease, *Jr Am Med Assoc*, 1910, iv, 1185
- ²⁸SONNENFELD, A Zur Frage der aplastischen Anämie, *Klin Wchnschr*, 1928 vii, 1585
- ²⁹BECART, A Remarques sur l'anémie pernicieuse et l'anémie aplastique, *Presse Med*, 1927, xxxv, 1538
- ³⁰MURPHY, F D, and McEACHERN, J M Aplastic anemia, *Wisc Med Jr*, 1926, xxv, 431
- ³¹McELROY, J B Differentiation of aplastic anemia and essential thrombocytopenia, its importance from therapeutic standpoint, *South Med Jr*, 1926, xix, 325
- ³²MARSH, H E Aplastic anemia, *Ann Clin Med*, 1924, iii, 162
- ³³GORKE, H Das Verhalten der Milz und des Knochenmarks und die Aussichten der Splenectomie bei der aplastischen Anämie, *Deutsch Arch f klin Med*, 1923, cxxxvi, 143
- ³⁴FALCONER, E. H, and MORRIS, L M Clinical comparisons of aplastic anemia, idiopathic purpura haemorrhagica and aleukemic leukemia based on studies of bone marrow, *Med Clin, N Am*, 1922, vi, 353
- ³⁵HIRSCHFIELD, H Ueber aplastische Anämie, *Folia haemat*, 1911, xii (1), 347

The Use of Sulphur for the Production of Fever in Peripheral Vascular Diseases*†

By LORENZ M. WALLER, M.D., and EDGAR V. ALLEN, M.D., F.A.C.P.,
Fellow in Medicine, The Mayo Foundation, Rochester, Minnesota

THE artificial induction of fever as a therapeutic measure in peripheral vascular disease has been well demonstrated. Its value rests on an increase in the circulation through the extremities, as demonstrated by determinations of cutaneous temperature. Brown and his co-workers have shown that the temperature of the skin increases to a far greater degree than the temperature of the mouth when fever is artificially induced, and have expressed the belief that this excessive increase in temperature is due to vasodilation. A vaccine consisting of *Eberthella typhi* (*Bacillus typhosus*), *Salmonella paratyphi* (*Bacillus paratyphosus A*), and *Salmonella schottmulleri* (*Bacillus paratyphosus B*), injected intravenously, serves admirably for the production of fever. Pain is also alleviated. There are four disadvantages in the use of this vaccine. (1) the occurrence of a chill, (2) the absence of the desirable part of the reaction after repeated injections, (3) certain untoward effects, and (4) the comparatively short duration of the fever. The effect of the typhoid "h" antigen (Eli Lilly and Com-

pany) was studied by Barker, who found that, following 314 injections given to sixty-three patients, chill occurred in only 27 per cent. Malaise was less marked. The use of this antigen marked a distinct advance in protein therapy, for chill is assumed to be conducive to vascular thrombosis,¹ and is not useful in the treatment of peripheral vascular disease. The untoward complications following intravenous injections of typhoid and paratyphoid vaccine have been emphasized by Hench². In a study of 10,000 injections in 2,500 cases he found unusual clinical phenomena subsequent to twenty injections in fourteen cases. Death occurred in three cases, a mortality of 0.12 per cent.

The history of the use of sulphur by injection has been reviewed recently by Mackay³. Subcutaneous injections were used by various investigators in 1907^{2,4,5}; these authors believed it lowered the temperature in bronchopneumonia and pulmonary tuberculosis. Intramuscular injections of sulphur in oil were first used by Schroeder⁶ in 1927 in the treatment of paresis. The literature regarding its use as a pyrogenic agent in syphilis, in other conditions of the nervous system and in

*Received for Publication April 3, 1931.
†From the Division of Medicine, The Mayo Clinic, Rochester, Minnesota.

rheumatic disease has since increased considerably^{4,6 9-12,15-18}

Our attention was directed by Mackay⁸ to the use of sulphur in producing artificial fever. The first injection was followed by such satisfactory results (the healing of chronic ulcers of the toe in a case of thromboangitis obliterans) that further investigation was carried out. We hoped it would have the following advantages (1) safety of use for persons of advanced age, (2) production of prolonged fever, and (3) absence of disagreeable sequelae following injection. The first two desiderata have been realized. Schroeder¹⁴ wrote that intramuscular injections of sulphur are without danger to infants, or to senile persons. Our series is small, but complications have not been noted in persons ranging in age from thirty-five to sixty-five years. Fever is present for a prolonged period as compared with that following injection of typhoid vaccine. In our experience, pain at the site of injection constitutes the single contraindication to the use of sulphur by the intramuscular route.

TECHNIC AND DOSAGE

A 2 per cent suspension of sulphur in olive oil* is injected deeply into the lateral aspect of the middle portion of the thigh. Warming and shaking of the suspension distributes the sulphur more evenly in the olive oil. Injections can be given every four or five days, using alternate thighs, and increasing the amount at each injection. The amount of the first injection is 1 c.c. Schroeder¹⁴ increased each

succeeding dose by 1 c.c. of 1 per cent suspension of sulphur in oil, giving as much as 10 c.c. at a single injection, and a course usually of ten injections. The greatest single dose we have used was 35 c.c. of a mixture of sulphur, 2 per cent, and olive oil. In our experience amounts in excess of 2 c.c. of the 2 per cent suspension have little, if any, advantage over the smaller amount and cause greater pain and more marked chill. Repeated injections of amounts of 2 c.c. have always been followed by satisfactory febrile response. Apparently, in paresis, results of treatment are dependent somewhat on the height of the temperature achieved. In persons with peripheral vascular disease, increases in the temperature of the skin are usually as great when the general body temperature is 15° to 2°C above normal as with greater increases. We have never given more than six injections in sixty days to one patient. Typhoid vaccine was given intravenously between injections of sulphur.

MATERIAL STUDIED AND EFFECTS OF SULPHUR INJECTED INTRAMUSCULARLY

The present study deals with fifteen patients who received thirty-two injections of sulphur. The group includes ten patients with thromboangitis obliterans, three with arteriosclerotic occlusive disease of the extremities, one with painful paresthesia, and one with sclerodactylia. In five additional cases, in which patients received twelve injections, detailed observations were not made. The ages of the patients varied from thirty to sixty-five years.

*Supplied by the Abbott Laboratories, Chicago

Fever began on an average of seven and six-tenths hours after injection. The greatest afebrile period following injection was thirteen and five-tenths hours; the shortest, seven hours (tabulation). Small doses of the suspension of sulphur tended to produce gradual increase in the temperature of the body; following larger amounts, the increase in temperature was more rapid. The average maximal temperature, following all injections, was 102.4°F . It is interesting that relationship is lacking between the amount injected and the maximal temperature attained. Five injections of 1 cc each produced an average maximal tem-

perature of 102.1°F , and the temperature, after fourteen injections of 2 cc each, was only 0.3°F greater, an increase of no appreciable value. The average duration of the fever following all injections was fifty hours (figure 1). Dosage had direct influence on the duration of the fever, which averaged only twenty-seven hours following injections of 1 cc and fifty-four hours following injections of 2 cc. Larger amounts of sulphur produced fever of even shorter duration. Increase in the cutaneous temperature of the extremities occurred in a manner similar to that ob-

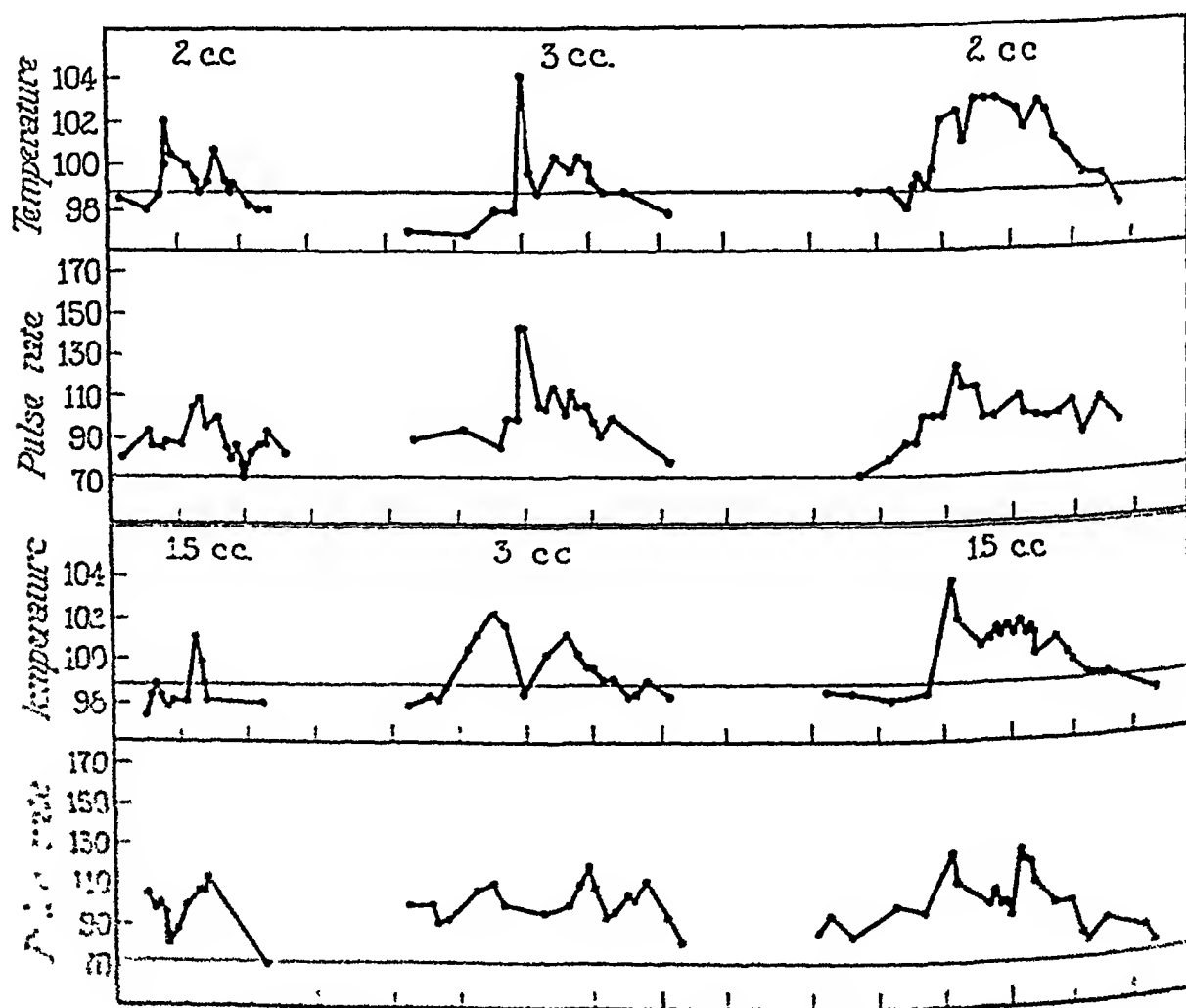


Fig. 1. Variations in the response of temperature and pulse rate to intramuscular injections of sulphur. The units laid off on the abscissa represent time in days.

served following intravenous injection of typhoid vaccine (figure 2)

Pain at the site of injection is the most disagreeable feature and the greatest objection to intramuscular injection of sulphur. Some patients complain little and others bitterly, but few wish the injection repeated, although none refused. In this regard, sulphur is far inferior to vaccine injected intravenously, for patients are unanimous in their preference to the discomfort caused by the vaccine as compared to that produced by sulphur.

The distress may be divided into continuous pain, and that which occurs only with movement of the extremity. The pain begins from one to three hours after the injection, and continues on an average of twenty-six hours before there is spontaneous relief. During an additional average period of fifty-one hours pain is present on moving the extremity, but absent when the leg is at rest (tabulation). This period occasions little complaint. The larger amounts of sulphur produced longer periods of pain.

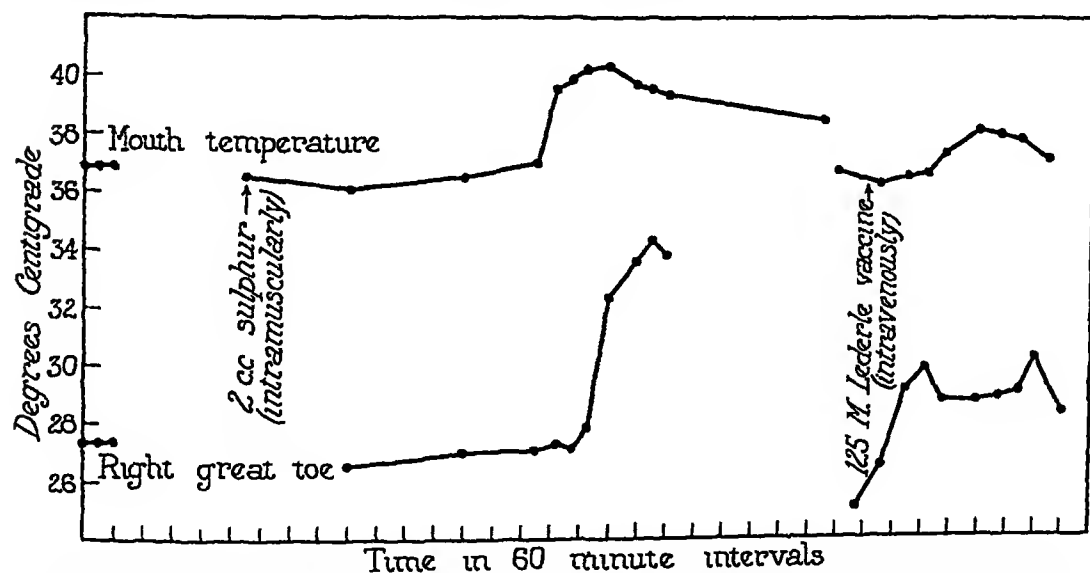


FIG 2 The response of the dermal temperature of the same patient following intramuscular injection of sulphur in oil and intravenous injection of typhoid vaccine

TABULATION

INTRAMUSCULAR INJECTION OF SULPHUR IN OLIVE OIL, IN PERIPHERAL VASCULAR DISEASE

Amount injected, cc	Number of injections	Afebrile period, hours	Average duration of fever, hours	Average maximal temperature, °F	Average time until onset of pain, hours	Average duration of severe local pain, hours	Average duration of all pain, hours
10	5	70	270	102.1	18	28	60
15	7	80	510	102.0	30	28	77
20	14	70	540	102.5	24	22	75
25	1	135	500	103.0	10	44	72
30	4	76	490	102.6	15	35	112
35	1	125	525	103.0	10	16	66

Our attempts to prevent the pain by injecting other materials with the sulphur and oil, although not extensive, were unsuccessful. A local anesthetic was tried on three occasions without benefit. As was expected, its effects had largely worn off before the pain had begun. The addition of 5 c.c. of the patient's blood to the injected sulphur and olive oil was likewise without beneficial effect. Prevention of the pain is highly desirable, and further attempts should be made. Mackay⁸ has advanced experimental data as evidence that sulphur produced its pyrogenetic effect through local destruction of muscle, and it is possible that substances which may be found to prevent the pain will also eliminate the sharp, fever-producing effects of the sulphur. More intensive study of this phase of the subject is essential.

Thirteen of the fifteen patients had indolent ulcers associated with mild to very severe regional pain. In all cases, some degree of relief of pain was noted. After all injections of the suspension of sulphur in excess of 1 c.c., pain was only about half as severe as before. In one instance pain in the region of an ulcer disappeared entirely, but in general sulphur lacked some of the pain-relieving properties of vaccine injected intravenously. This study demonstrates that the fever and not the vaccine alone is responsible for the relief of pain with the patient at rest, in peripheral vascular disease. One patient with painful paresthesia of the feet did not receive relief from intramuscular injections of sulphur; later the pain was shown to be of central origin, for spinal anesthesia, with

complete motor and sensory paralysis, likewise failed to give relief.

Chill occurred following seventeen of the thirty-two injections of suspension of sulphur. In ten of these instances the chill was graded 1 in severity; in four it was graded 2; in two it was graded 3, and in one it was grade 4. Twenty-six injections of suspensions in amounts of 2 c.c. or less were followed by chill in thirteen instances (50 per cent), but the chill was of minor degree (graded 1 or 2) in all but one instance. Patients generally complained but little of the chill and it was not a contraindication to the use of sulphur.

An increase in the number of leukocytes followed the injection of sulphur in all the cases studied. Frequently they numbered as many as 45,000 for each cubic millimeter of blood. Study of the blood smears revealed definite increase in the percentage of neutrophilic leukocytes. The number and percentage of the leukocytes in the blood reached normal values on an average of ninety-eight hours following injection of sulphur.

It is difficult to evaluate the effect on the ulcers of sulphur injected intramuscularly, for typhoid vaccine was given intravenously and local applications were also used in most of the cases. In two cases of thromboangiitis obliterans with gangrenous ulcers, in which courses of vaccine were administered, the condition of the ulcers improved after the first injection of sulphur and the lesions were healed in three weeks.

In five cases of thromboangiitis obliterans, with severe ulcers or gangrene, the course of the disease was

unmodified by treatment with vaccine and sulphur, and amputation was necessary. Five patients were spared amputation. In one case of arteriosclerosis of the extremities, amputation was later necessary. The condition of one patient improved sufficiently to allow successful amputation of a toe, that of one patient was unchanged during a short period of observation. The ulcers on the heels of one patient with sclerodactylia healed slowly under treatment with combined sulphur and vaccine. In general, the results of injections of sulphur on ulcers or gangrene, in patients with peripheral vascular disease, were equal to and occasionally exceeded the results following intravenous injections of vaccine. The temperature of the skin increased following injections of sulphur in much the same manner as it increased following intravenous injections of vaccine.

THE METHOD OF ACTION OF INTRAMUSCULAR INJECTIONS OF SULPHUR

Mackay has reviewed the opinions as to the mechanism by which sulphur injected intramuscularly produces fever. Impressed by the theoretic nature of these opinions he approached the problem experimentally. Rabbits were used, but even with doses, based on body weight, which exceeded by thirty times those used in man, fever was not produced. Sections taken from the region injected, twenty-four and forty-eight hours after injection, gave evidence of profound necrosis and marked inflammatory reaction, large numbers of polymorphonuclear leukocytes and a few lymphocytes were present. Less striation of the

muscle fibers, with fragmentation and degeneration, was observed. Sections, taken thirteen days following injection, gave evidence of subsidence of the acute inflammatory process; there was evidence of proliferation of fibroblasts, and foreign-body giant cells and regenerating muscle fibers were seen. Olive oil was not essential to the production of the inflammatory reaction, for sulphur in a mixture of acacia, 1 per cent, in physiologic solution of sodium chloride produced the same pathologic changes as sulphur in olive oil. As a result of his experimental studies, Mackay expressed the belief that the fever which follows intramuscular injection of sulphur is a result of a reaction to protein liberated from the patient's own muscle, or that it is a result of the action of hydrogen sulphide formed from sulphur in the tissues. As Mackay logically pointed out, the afebrile period following injection, the increasing amounts of sulphur necessary, and the pathologic changes induced, argue for such a mechanism as was postulated by him.

COMMENT

The ideal pyrogenetic agent would be one which would produce fever of as long duration as is desired without disagreeable or harmful local or general reactions. Unfortunately such an agent is as yet unavailable. Intravenously injected vaccine, although a very valuable therapeutic aid, has the disadvantages that there is slight danger of complications, and that the fever is of comparatively short duration. Sulphur injected intramuscularly is superior to vaccine in that it can be used with safety for patients of advanced

age and in that the fever is of longer duration. It is inferior to vaccine because of its reaction and because of the distress occasioned at the site of the injection. The patient's attitude toward injection of sulphur varies; some patients request repeated injection because of favorable results; some extremely dislike, and nearly refuse, injection because of the pain induced.

Each patient should be informed of the pain before the injection is given, morphine or codeine should be used freely during the period of acute distress. Antipyretics, such as acetylsalicylic acid, should be avoided because of their effect in lowering temperature. As yet no permanent impairment of muscle function as a result of repeated injections has been reported even by Schroeder,^{13,14} who has had extensive experience. On the basis of Mackay's experimental work, such changes in muscle function can be reasonably expected provided injections are repeated a sufficient number of times. For our purpose, in the treatment of peripheral vascular disease, a smaller number of injections than that which Schroeder gave without detrimental effects is usually sufficient. Increasing doses were not necessary for one patient who received six injections.

The evidence that sulphur itself is of therapeutic value in peripheral vascular disease is largely lacking in this study. Because of the pain at the site of injection, the use of intramuscular injections of sulphur in the future probably will be reserved for persons to whom the distress is not severe, for those who are temporarily insensitive to typhoid vaccine, and for those of

advanced age. We cannot substantiate Mackay's observations that persons who do not respond well to vaccine do not respond to sulphur. Our experience is the opposite, and sulphur is commonly used when typhoid vaccine is ineffectual.

SUMMARY AND CONCLUSIONS

Observations were made on pain at the site of injection, on relief of pain in ulcerated or gangrenous regions, on healing of ulcers, on height and duration of fever, and on chill and leukocytosis in fifteen cases of peripheral vascular disease, in which thirty-two intramuscular injections of sulphur, 2 per cent, in olive oil were given. In five additional cases twelve injections were given, but detailed observations were not made.

Fever began about seven hours after the injection; the temperature reached an average maximal level of 102°F, and lasted an average of fifty hours. Chills occurred following approximately 50 per cent of the injections, but they were mild when doses of suspension of sulphur of 1.5 cc., or 2 cc., were given.

The most satisfactory dose in treatment of peripheral vascular disease was 1.5 c.c. or 2 c.c. Greater amounts were rarely necessary to produce effect, even later in the course of the injections.

Clinical improvement was as marked following intramuscular injection of sulphur as that induced by intravenous injection of typhoid vaccine, and occasionally it was more striking.

The pain at the site of the injection varied from moderate to severe and constituted the greatest disability.

to intramuscular injection of sulphur in olive oil

Sulphur in olive oil, injected intramuscularly, in the treatment of peripheral vascular disease, is most satisfac-

tory for persons of advanced age, for those who are resistant to treatment by vaccine, and for those in whom the pain from the injection is not excessive

BIBLIOGRAPHY

- ¹BARKER, N W Typhoid "h" antigen further observations on nonspecific protein therapy in peripheral vascular disease, *Proc Staff Meetings of Mayo Clinic*, 1930, v, 267-269
- ²BORY, LOUIS Sur l'introduction du soufre dans l'organisme par la voie sous-cutanée, *Compt-rend Soc de biol*, 1907, lxxiii, 512-514
- ³BROWN, G E, ALLEN, E V, and MAHORNER, H R *Thrombo-angitis obliterans*, 1928, W B Saunders Company, Philadelphia
- ⁴DELEHAYE and PIOT A propos de l'introduction du soufre sous la peau, *Compt-rend Soc de biol*, 1907, lxxiii, 601
- ⁵FLEIG, C Le soufre en nature insoluble, colloïdal ou à l'état naissant en injections sous-cutanées et intra-veineuses, *Compt-rend Soc d biol*, 1907, lxxiii, 625-627
- ⁶HARRIS, N G Treatment of general paralysis of the insane by injection of sulphur, *Lancet*, 1930, i, 1068-1069
- ⁷HENCH, P S Usual and unusual reactions to protein therapy (intravenous typhoid vaccine), *Proc Staff Meetings of Mayo Clinic*, 1930, v 206-208
- ⁸MACKAY, R P The use of sulphur for the production of fever, *Arch Neurol and Psychiat*, (In press)
- ⁹MARCUSE, HARRY, and KALLMAN, FRANZ Zur Sulphosinbehandlung der Paralyse und Schizophrenie, *Nervenarzt*, 1929, ii, 149-153
- ¹⁰MEYER-BISCH, ROBERT Über die Behandlung chronisch deformierender Gelenkerkrankungen mit Schwefel, *Klin Wchnschr*, 1922, i, 575-578
- ¹¹PATTERSON, W G, and SWITZER, S R L Sulfosin therapy in general paralysis of insane, *Lancet*, 1930, ii, 348-349
- ¹²SCHROEDER, KNUD Über Schwefelbehandlung der Dementia paralytica und anderer metaluetischer Affektionen des Zentralnervensystems, *Klin Wchnschr*, 1927, vi, 2189-2191
- ¹³SCHROEDER, KNUD Über Sulfosinbehandlung von Nervensyphilis und anderen syphilitischen Erkrankungen, *Klin Wchnschr*, 1928, vii, 1636-1639
- ¹⁴SCHROEDER, KNUD The sulfosin treatment of general paralysis, *Lancet*, 1929, ii, 1081-1084
- ¹⁵SHILLOCK, W H The pyrogenetic action of sulphur in olive oil, *Lancet*, 1930, ii, 347-348
- ¹⁶SPIRO, PAUL Zur unspezifischen Reizkörpertherapie chronischer Gelenkerkrankungen, *Deutsch med Wchnschr*, 1927, liii, 914-915
- ¹⁷TUTUJI, D F Subcutaneous injection of colloidal sulphur in neuritis, *Lancet*, 1925, ii, 408
- ¹⁸WINKLER, LUDWIG Über Schwefeltherapie der Optikusatrophie, *Wien klin Wchnschr*, 1928, xli, 374-375

Mediastinal Displacement in Pneumothorax*†

By W. C. POLLOCK, M.D., Major, Medical Corps, U. S. Army
Denver, Colorado

ROENTGENOLOGICAL study of pneumothoraces, whether artificially induced or spontaneous, frequently reveals mediastinal displacement. This displacement may be of the superior anterior mediastinum, of the inferior or of the entire mediastinum. The displacement associated with artificial pneumothorax therapy or in spontaneous cases is due to a disturbance of the normal physiological intrathoracic equilibrium. The degree of displacement is not in all cases proportionate to the change in intrathoracic equilibrium because of factors that will be discussed later.

Mediastinal displacement is observed in cases of pulmonary tuberculosis unassociated with pneumothorax and in cases where pneumothorax no longer exists, but this type of displacement will not be discussed in this paper.

The bulging or displacement of the superior anterior mediastinum is the type observed during fluoroscopic study of artificially induced pneumothorax cases. It is frequently noted during such study that the contra-

lateral lung is encroached upon by the pneumothorax cavity bounded by the mediastinal pleura. This condition is ordinarily detected only during fluoroscopic study and is not observed on the routine x-ray plate. As stated by Sewell¹ the bulging only eventuates during the phase of expiration and so far as it affects the respiration, it should operate to aid in the expiratory contraction of the lung and in the expulsion of its foul residual air. Conversely, the inspiratory swing of the mediastinum toward the middle line allows, if it does not assist, the renewal of air of unusual oxygenated power to the full capacity of the contralateral lung.

Mediastinal displacement of the type influenced by the phases of respiration in artificial pneumothorax is usually in right sided pneumothorax the mediastinal herniation or bulging invading the left chest. The reverse has been noted, but is a rather rare occurrence. When pneumothorax is induced on the left, the position of the esophagus obstructs mediastinal displacement from left to right. The displacement from right to left is possible because of an anatomical wedge between the two pleural cavities due to the fact that the aorta and the compressed esophagus lie somewhat

*From the Medical Service, Fitzsimons General Hospital. Received for publication, March 3, 1931.

†This paper is the property of the Surgeon General's Office and is loaned to you for personal use only. It is not to be distributed outside your institution.

left of the vertebral column. Displacement does not occur in most cases because the mediastinum is fixed, or practically fixed, by adhesions and thickening of the pleura. This condition is frequently the case in older adults and in long standing cases of pulmonary tuberculosis, and for this reason mediastinal displacements are most frequently observed in earlier

cases of tuberculosis in younger adults where mediastinal mobility is not lessened by pleural thickening and adhesions.

Figure 1 illustrates the type of displacement under discussion, as shown on the x-ray plate. It is observed that the mediastinal pleura runs from the inner third of the clavicle downward to become continuous with the cardiac

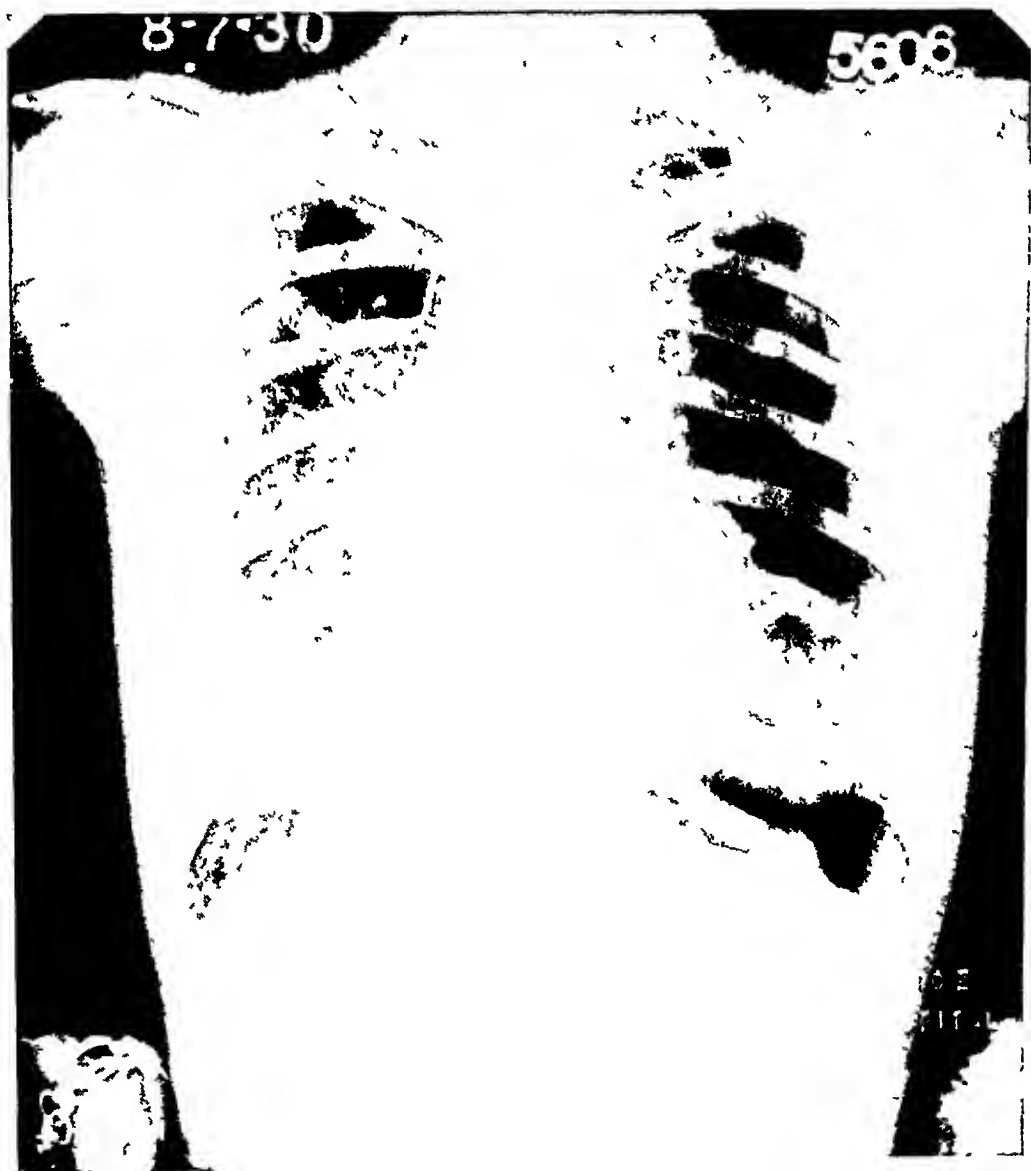


FIG. 1

shadow at about the level of the third rib. As stated, routine x-ray plates seldom show the condition because they are usually made during the phase of inspiration, and during this phase the mediastinum moved toward the pneumothorax cavity. It is during fluoroscopy when the mediastinum can be observed, as to position, during inspiration and expiration that the apparent encroachment upon the contralateral lung is observed.

The condition is not a serious one and can hardly be classified as a complication. It is not associated with cardio-respiratory embarrassment. The encroachment as can be seen by lateral x-ray plates is not upon the lateral lung surface; but only upon its anterior surface. There is no lateral compression of the lung, but rather a slight anterior-posterior compression. The condition is of minor clinical significance and occurs in the presence of negative intrathoracic pressure.

Infrequently there is observed a superior anterior mediastinal displacement of an entirely different character. The right upper lobe of the lung herniates into the left chest, the hernial sac consisting of the mediastinal pleura. The hernia remains fixed in the left chest uninfluenced by respiration. There may be present respiratory embarrassment with a pressure sense to the stage of discomfort and the condition is considered of clinical significance. This condition is usually associated with positive pressure in the pneumothorax cavity of the right chest.

Figure 2 shows a hernia of the right upper lobe of the lung into the left chest. The plate is made during expiration yet the hernia en-

croaches upon the contralateral lung. Respiration produced no movement of the hernia. The mediastinum, except for the anatomically weak superior anterior mediastinum, was relatively fixed. The plate is of a patient who received a refill of gas in an eastern city prior to journeying to Denver, Colorado. The eastern city being near sea level and Denver being over five thousand feet in altitude, it is estimated that the intrathoracic pressure was increased approximately twenty per cent. The increase was sufficient to produce a moderately high positive intrathoracic pressure which was sufficient to push the firm fibrous right upper lobe into the anatomically weak area of the mediastinum. Ordinarily mediastinal bulging occurs in cases where the pleura is relatively free and elastic, but as pointed out by Dummerst and Brette² it may occur in cases with relatively nonelastic pleura when there is overstrong pressure in the pneumothorax cavity.

In this case the mediastinum must have been relatively nonelastic and fixed since the case is one of long standing pulmonary tuberculosis in an adult 42 years of age. Artificial pneumothorax had been used as an adjunct in his treatment for over one year. There were numerous band-like adhesions over the lower half of the lung and at autopsy there was found one fibrous adhesion running from the visceral pleura to the mediastinal pleura.

In general, the degree of displacement depends upon flexibility of the mediastinum, the amount of intrathoracic pressure in the pneumothorax

space and the relative fixation of the mediastinal contents

The factor of importance in this case was that of intrathoracic pressure. The removal of 800 c.c. of air from the right chest completely reduced the herniation of the lung with considerable reduction of the cardio-respiratory embarrassment. During fluoroscopy

the mediastinal line could not be observed in the left chest, even during forced expiration.

Figure 3 shows the change produced by removal of air. The right upper lobe of the lung can now be seen in the right chest. The right lung has re-expanded somewhat, causing an elevation of the fluid level and the

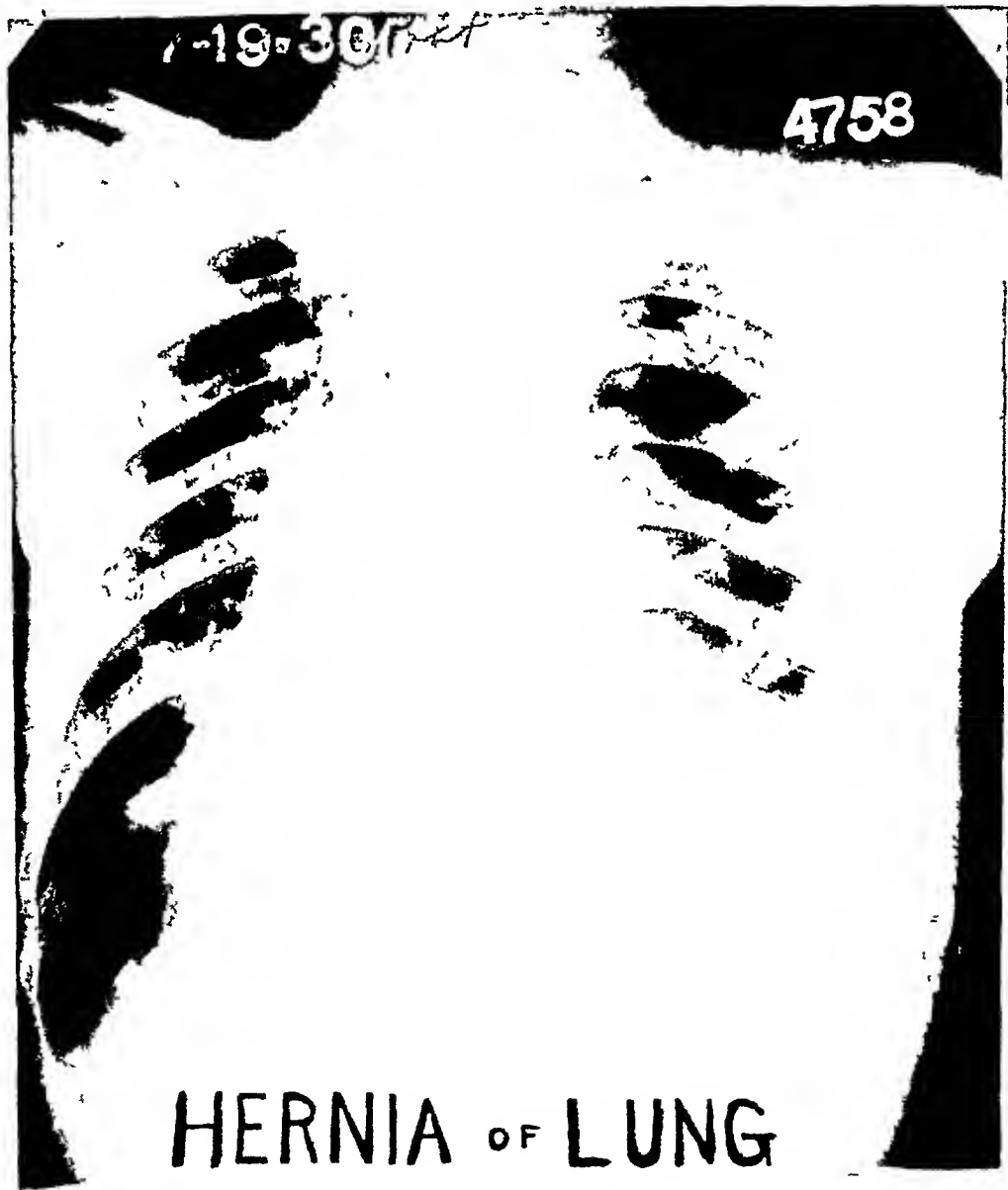


FIG 2 Hernia of right upper lobe into the left chest

mediastinal bulging into the left chest through the anterior superior mediastinum no longer exists

We wish to emphasize the fact that such a condition is entirely different from the swinging superior mediastinum noted in young adults earlier in the employment of pneumothorax.

In this case the mediastinal hernia contained a lobe of the lung from the opposite chest with a sufficient encroachment upon the contralateral lung to cause respiratory embarrassment. The hernia did not recede during inspiration and did not increase its encroachment during expiration;



FIG. 1. Mediastinal hernia containing a lobe of the lung from the opposite chest, produced by removal of the

therefore it hindered oxygenation of the contralateral lung

As stated by Stivelman, Hennell and Golembe³ the size of the untreated hemithorax will be proportionately decreased and because of this its intrapleural pressure will be proportionately less negative. The intrathoracic pressure on the untreated side will be proportionately increased and will be equal to the intrathoracic pressure on the pneumothorax side minus the elastic recoil of the stretched mediastinum.

In our case under discussion the decrease in negative pressure of the untreated hemithorax was greater than usually observed because of the ab-

sence of an elastic recoil of the mediastinum.

A similar case is shown by figure 4. In this case there is also an actual hernia of the lung through the superior mediastinum. The plate is of a case of a closed spontaneous pneumothorax superimposed upon an artificial pneumothorax. Figure 4a shows the specimen removed at autopsy. The portion of the lung invading the opposite chest stands out as distinct protrusion from the rest of the lung.

In cases with a relatively mobile mediastinum there may exist a marked degree of displacement without aggravating cardiorespiratory embarrassment. In the absence of pleuroperi-



FIG 4. Hernia of lung through the upper mediastinum

cardial adhesions the heart may be converted into a complete dextrocardia without cardiac symptoms. We are now referring to the type of mediastinal displacement in which the entire mediastinum and its contents are pushed to one side. This condition is observed in spontaneous pneumothoraces with positive pressure, usually associated with pleural exudate. Whether or not there are acute symptoms depends somewhat upon the rapidity of the displacement. If the lung collapse is rapid in a case untreated by pneumothorax the symptoms are usually acute. Should the spontaneous

pneumothorax be superimposed upon a previously existing artificially induced pneumothorax the symptoms may be extremely mild. In fact, the accident may happen and be unknown to the patient or his physician until it is detected by fluoroscopy prior to a contemplated pneumothorax refill. Apparently this type of displacement may occur to the right as well as to the left. However, the left to right displacement requires greater pressure and the degree of displacement is less.

Figures 5 and 6 show this type of displacement. These plates are of spontaneous pneumothoraces superim-



posed upon induced pneumothoraces, both showing pleural exudate. Both cases are of long standing and have few symptoms when the pleural exudate is removed at frequent intervals.

It has been noted in the earlier thoracenteses of such cases that the mediastinum returns to a practically normal position. Later in the treatment the mediastinum tends to become fixed in its displaced position and

shows little tendency to return to its normal position after removal of pleural exudate. The same is true of the swinging movement of the mediastinum during respiration which also tends to become less and less and finally may become fixed. As the mediastinum becomes fixed in the opposite chest there then appears more respiratory embarrassment and sensation of pressure, relieved by removal of air with return of the mediastinum to nor-



FIG 5 Displacement produced by spontaneous pneumothorax superimposed upon induced pneumothorax, with pleural exudate

mal position In these two cases the lung remained collapsed because of a small bronchial fistula which existed for some time without infection of the pleural exudate Bronchial fistulae were proven to exist by the introduction of dye into the chest cavity and noting same to appear in the sputum

This type of case sooner or later becomes a surgical case because of the development of pyothorax In some

instances in which the fistula is small and tortuous and requires coughing attacks to force air from the respiratory tract to the pneumothorax space, there may be considerable interval before the pleural exudate becomes infected

Another type of mediastinal displacement is the respiratory deviation of the entire mediastinum noted during fluoroscopy. This deviation, when

8-19-30



6-2-30



observed during forceful respiration, is rather astounding in some cases. It is believed that many who have not given particular attention to movements of the mediastinum would be rather surprised to note the degree of respiratory deviation in certain cases. The mediastinum in instances seems to encroach upon the contralateral lung to over one-half of its diameter. An observer may in haste conclude that this type of displacement is the factor

of respiratory embarrassment. However, rather marked displacement is frequently seen in cases without symptoms. Let us again point out, as is shown by figures 7 and 8, the position of the mediastinum with reference to the phases of respiration. It will be noted that the mediastinum makes its encroachment upon the contralateral lung during the phase of expiration and recedes to the pneumothorax side on inspiration. Marked deviation is

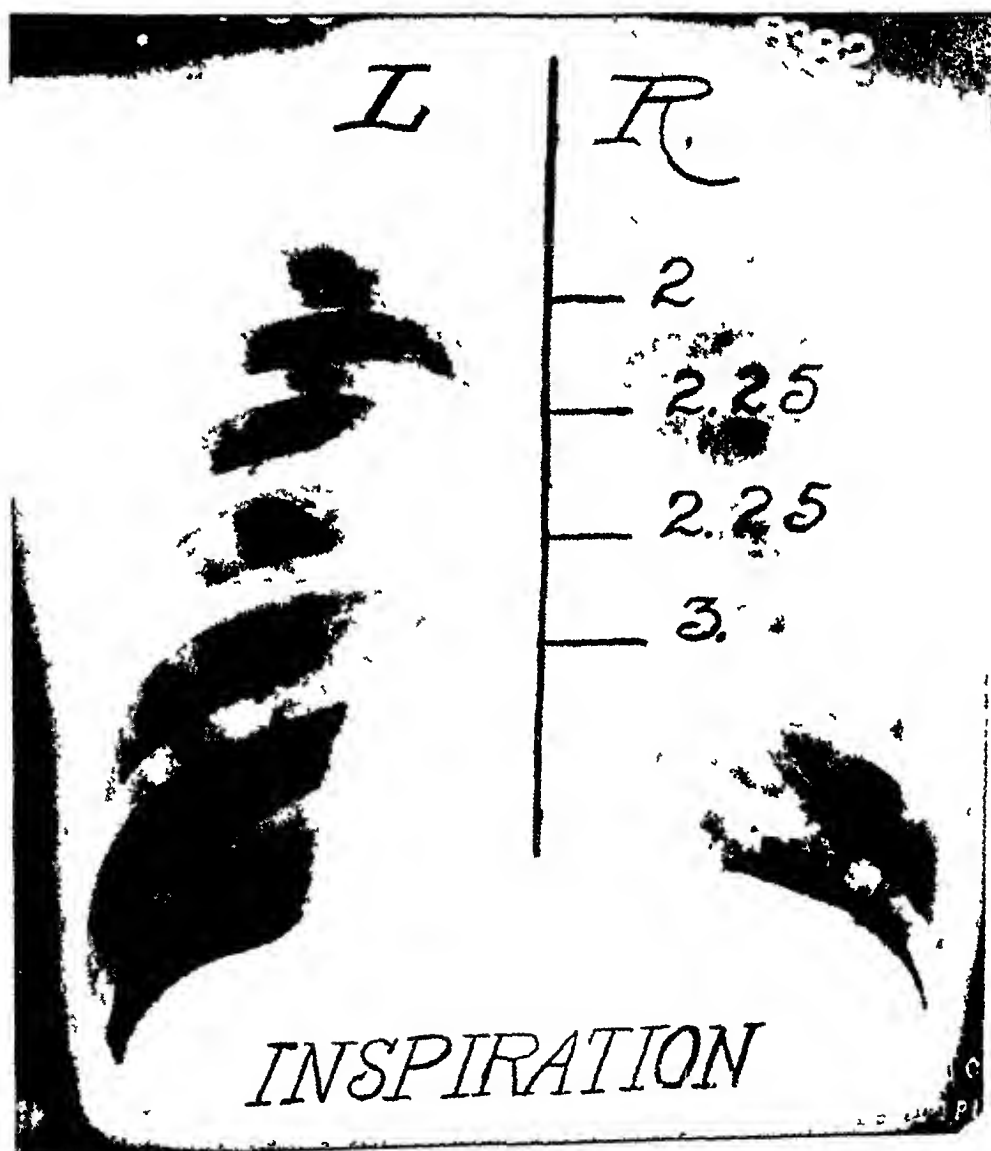
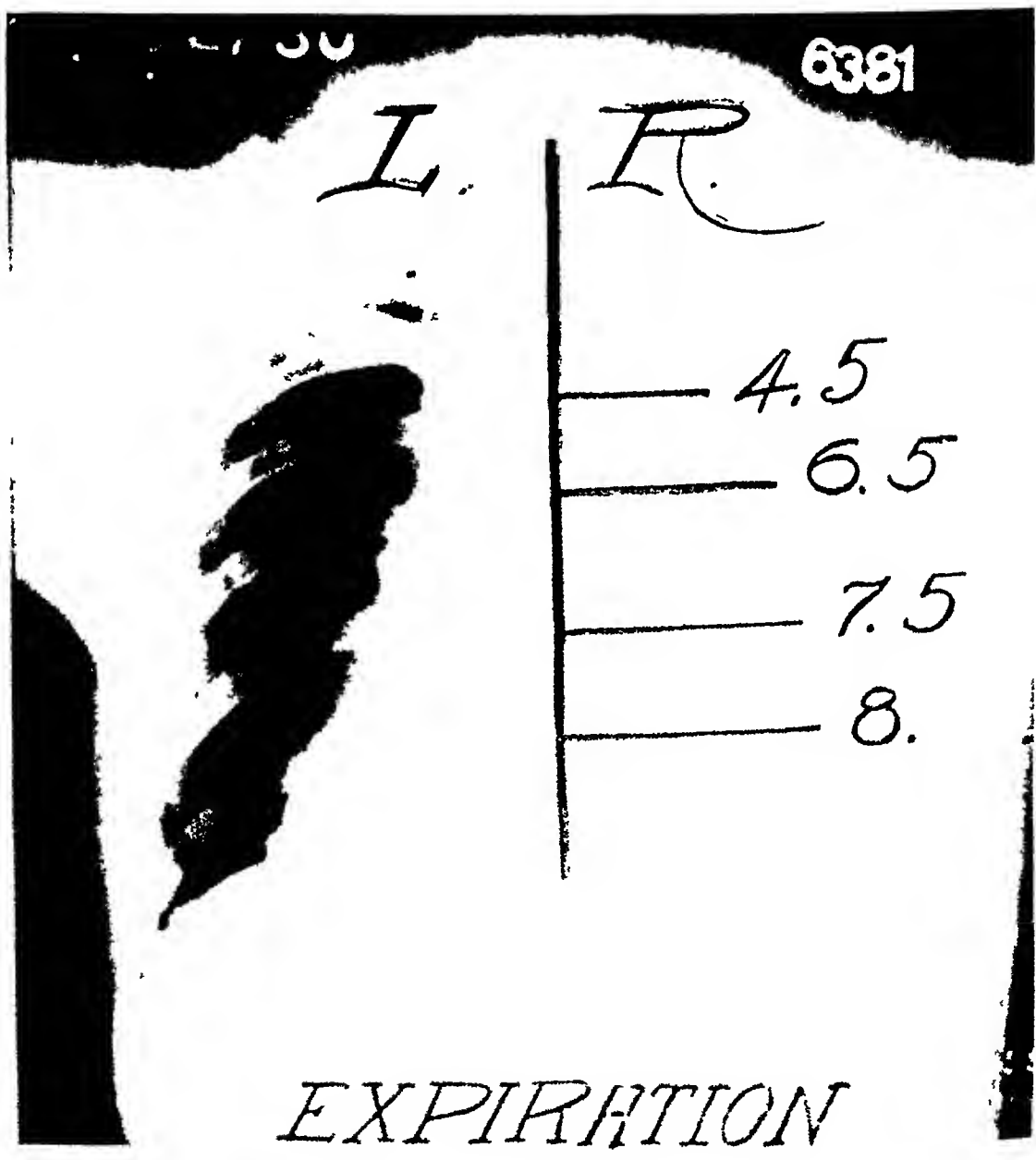


FIG 7 Mediastinal relations during inspiration

usually observed in younger adults earlier in the treatment by artificial pneumothorax. It has also been observed that as pneumothorax treatment is continued the mediastinal mobility tends to become less and less, finally becoming relatively fixed. This is due to the fact that the pleura becomes less elastic, and somewhat thickened under continuous pneumothorax treatment. Von Muralt¹ calls attention to the positive assistance given the respiratory

function of the contralateral lung by the mediastinal deviation in therapeutic pneumothoraces. He also states that the situation here is the exact opposite to that found in wide open pneumothorax both as to mechanics and vital effects.

In cases of mediastinal deviation so well observed during respiration at the time of routine fluoroscopy there also exist characteristic manometer readings. The mediastinum is so flexible



that it is gradually displaced by the introduction of air into the pneumothorax cavity. This fact was discussed by Parfitt.¹ According to Boyle's Law, "The temperature remaining the same, the volume of a given quantity of gas is inversely as the pressure which it bears." This would mean that with rigid pneumothorax cavity walls there should be a proportionate change in the manometer reading following the introduction of each 100 c.c. of gas. It is not unusual, however, to observe that the manometer reading may show little change during the introduction of the first several 100 c.c. of gas. The interpretation of this is that the introduction of gas does not proportionately increase the pressure because the pneumothorax cavity has enlarged by mediastinal displacement.

Dumarest and Brette² state that disturbance of the mediastinum and the delicate organs it encloses causes functional trouble, such as dyspnea on exertion, and tachycardia uncomfortable for the patient, and may lead to a dislocation of the mediastinal partition without pulmonary compression being either complete or effective.

We know that rather marked deviation may occur without symptoms. There must be other factors than the displacement in itself which result in functional trouble.

With an elastic mediastinum, free of adhesions, in the young adult, where the pressure in the pneumothorax cavity is maintained well on the negative side there are usually no symptoms resulting from mediastinal deviation.

The most pronounced symptoms have been observed in left pneumothorax with pleuro-pericardial adhesions, and in longer standing cases with thickened pleura where pressure is employed to stretch adhesions for better collapse of cavitations. It has been our experience that functional symptoms are more apparent where pressure is applied to a relatively fixed mediastinum than where there is considerable deviation of a flexible mediastinum under negative pressure.

The movements of the mediastinum are called, by Stivelman, Hennell and Golembe³ "Movements of Balance." They state that the intrathoracic pressure is established in pneumothorax as under all normal conditions. The change in pressure in one hemithorax must be balanced by approximate changes on the opposite side, and it is in response to this fundamental principle that certain so-called "Movements of Balance" take place in the chest cavity in pneumothorax.

When both hemithoraces are exactly alike in capacity and both lungs are equally expanded to fill them, there would be comparatively little or no disturbance in the relative position of the mediastinum during inspiration. On the other hand, supposing one hemithorax to be relatively immobile and the other hemithorax capable of large expansion, we can easily see how, during inspiration, a movable mediastinum would be shifted toward the large hemithorax because of the rapidly increasing negative pressure developed therein. It is believed that some understanding of the so-called "Movement of Balance" in pneumothorax is essential. The physics of

the phenomenon may upon superficial consideration appear rather confusing, but when one fully appreciates that we are dealing with differences in pressure and that the pressure changes with the phases of respiration, the movements noted under the fluoroscope are then understood. In fact, the phenomenon becomes simple. Appreciation of such movements leads to a clearer understanding of Kienboeck's phenomenon and other forms of paradoxical breathing.

We have been unable to demonstrate true paradoxical diaphragmatic breathing in artificially induced pneumothorax. The diaphragm has been noted to be lower than normal, may appear irregular in passing from the phase of expiration to inspiration and may appear to present a paradoxical movement of slight amplitude when the intrathoracic pressure on the pneumothorax side reaches a positive pressure at expiration. The apparent paradoxical movement disappears when the pressure is decreased or when position of the patient is changed toward the pneumothorax side.

True paradoxical diaphragmatic breathing is observed in pneumothorax cases when there is a paralysis of the diaphragm.

With the principle of "Movements of Balance" in mind an attempt was made to determine the approximate degree of incapacity of respiratory movement of the hemithorax required to produce movements of balance. Immobilization of the hemithorax by fixation of chest wall in a normal individual caused no movement of the chest. Fixation of the chest wall in a patient with a paralyzed hemithorax

increased movement of the diaphragm. To prevent compensatory diaphragmatic breathing on the side of fixation, an individual was selected who had a paralyzed diaphragm due to phrenic exeresis. The individual selected showed a movement of the mediastinum during forced respiration. The right chest was immobilized, and x-ray made during full inspiration and another during full expiration, with the result that the mediastinum was found to remain practically stationary. The cardiac shadow was found to move through a distance of only nine-tenths of a centimeter.

It was found that procedures as outlined above were insufficient to produce mediastinal movements as frequently observed in artificial pneumothorax cases where lung compression ranges from twenty-five to fifty per cent.

SUMMARY

A disturbance of the normal physiological intrathoracic pressure during the course of artificial pneumothorax therapy may produce mediastinal displacement when the mediastinum is sufficiently flexible.

Mediastinal displacements extending into the contralateral lung during the phase of expiration are of mechanical significance. However, fixed displacements in the presence of a relatively nonelastic mediastinum are produced by over strong pressure in the pneumothorax cavity may give rise to respiratory embarrassment in the sense of pressure to the stage of discomfort. A reduction of the displacement results in comfort to the patient. Mediastinal displacement is

upon flexibility of the mediastinum, the intrathoracic pressure in the pneumothorax cavity, and the relative fixation of the mediastinal contents

usually occurs in younger adults early in artificial pneumothorax treatment, and the mediastinum tends to become less and less flexible as pneumothorax therapy is continued

A relatively flexible mediastinum

REFERENCES

- ¹SWAN, H. A critique of artificial pneumothorax in pulmonary tuberculosis, *Amer Rev Tuberc*, 1929, xviii, 117-201
- ²DUMARFST, F., and BRLETT, P. Mediastinal hernia in artificial pneumothorax, *Abstracts Amer Rev Tuberc Sect*, 1925, xi, 18-19
- ³STEFANIAN, B. P., HENNILL, H., and GOLEMB, H. Clinical significance of altered intrathoracic equilibrium in pneumothorax with special reference to optimal pressures, *Jr Am Med Assoc*, lxxviii, 1450-1452
- ⁴MURALT, V. Der kunstliche Pneumothorax, 1922
- ⁵PARRITT, C. D. The adjustment of pressures in induced pneumothorax with especial regard to the mobility of the mediastinum as indicated by manometer *Arch Int Med*, 1916, xvii, 646-658

Treatment of Recurrent Erysipelas*

By HAROLD L. AMOSS, M D, F A C P, *Durham, N C*

RECRUDESCENCES and relapses are not uncommon in streptococcal infections. In facial erysipelas, the lesion may subside and the skin become almost normal but suddenly within a few hours all the signs and symptoms may return. When this occurs in facial erysipelas we have learned to suspect the presence of sinusitis. An example will illustrate this type of recrudescence.

Italian girl, aged sixteen years, admitted on the sixth day of an erysipelas infection involving both sides of the face, marked cervical adenitis and pharyngitis with obstruction to breathing. There was tenderness over both maxillary sinuses.

The symptoms of toxemia disappeared quickly after the administration of erysipelas antitoxin and the lesion began to recede but the fever did not abate for three days and then endured to a mild degree. Ten days later, both maxillary sinuses were irrigated and from the pus there was obtained a pure culture of beta hemolytic streptococci. The temperature came to normal and later rose presaging severe serum sickness. Suddenly on the twenty-seventh day after onset, the patient complained of chills, sensations and headache and the temperature rose to 104°F. There was a rapid return of the lesion confined strictly to the areas previously involved but the skin was less shiny. The leukocyte count rose rapidly from 8000 to 15000. The tonsils and cervical glands were not noticeably enlarged or tender. The nasal

passages were completely stopped by dried mucosanguineous discharges. After shrinking and the removal of a large amount of bloody pus by suction, the patient felt much improved, the temperature fell sharply to normal within four hours, and within eight hours the erythema and swelling of the face had disappeared. The leukocyte count became normal in twenty-four hours. Eighteen hours later the succession of events was repeated exactly, and the patient was discharged well, eight days later and has remained so for one year.

In other cases, treated with serum the skin previously involved and showing almost complete return to normal may become red, tender and swollen but not thick and brawny. Because of general glandular enlargement, arthritis and urticaria in other parts of the body and the failure in every case to cultivate streptococci from the skin, and also the subsidence of the lesion and the general signs, we regard this apparent recrudescence as a manifestation of serum sickness.

There is still another type of true recurring erysipelas in which the typical signs and symptoms recur after several months or years. Usually the succeeding attacks are milder than the first but recurring erysipelas may be severe and attacks vary in intensity. We have studied 25 such cases in the Danville State Hospital for the Insane. In eight of these patients there was no reaction to the endermal injection of 0.1 cc. of

*Presented at the 1934 Meeting of the American College of Physicians, Miami Beach, Florida.

trate of the broth culture of the erysipelas hemolytic streptococci. Of the remaining 17, three died of other causes during the year of observation. There remained 14 patients who had experienced from 2 to 5 attacks of erysipelas during the preceding two years and who, at the beginning of the study, reacted to one or more of the test strains. Without varying any other factor these 14 patients were given subcutaneously increasing doses of the streptococcus filtrate and tested for sensitivity every six months for two years. Ten patients reacted to both allergins. Further immunization with the second allergin reduced the sensitivity in all but three of them. Thus three patients remained sensitive and of these, two had a mild recurrent attack of erysipelas during the two years of observation.

In summary 14 patients had 35 attacks of erysipelas in the two years before the immunizing experiment but among the eleven patients surviving the two years of observation and immunization there occurred only two attacks of erysipelas. Apparently the injection of streptallergen in these patients had a decided effect on the number and intensity of the recurring attacks.

The main purpose of this paper is to describe our experiences in a third type of so called recurrent erysipelas of the leg. These cases really belong to the category of cellulitis. As a preface to a description of chronic recurring cases there will be presented an acute case which initiated the reasoning approaching the allergic concept.

Case I Italian, male, 28, toes crushed. With dressings, the superficial lacerations

healed in six weeks and the patient was ambulant for ten days. Suddenly, four days before coming to us, the dorsum of the foot became swollen, hot and painful, and with a high fever, the patient experienced chills, nausea and anorexia. He was admitted to the ward with cellulitis of the foot and leg, femoral and inguinal adenitis. The symptoms had increased. He was given intravenously and intramuscularly erysipelas antiserum. Within ten hours, the temperature was normal and the lesion began to recede so that within three days it had entirely subsided. Beta hemolytic streptococci were obtained in pure culture from a fluctuant tumor on the under surface of the second toe and from the skin lesion on the leg. The abscess on his foot healed slowly and the patient was discharged six and a half weeks after admission, as well. Four days later he noticed a slight and offensive discharge from about his toes on both feet but there were no constitutional symptoms. He walked without discomfort and seemed well for one month when he lost his appetite and felt unable to work. Four days later, he had suddenly a chill and within a few hours, the swelling, redness and pain appeared in the area previously involved. He was readmitted with a temperature of 103.6°, WBC 19,000, and presented a picture practically identical to that of the previous admission, except that the skin over the involved area was a darker red. Cultures at this time were positive from the recurring abscess under the second toe but skin cultures from the involved area were negative. The abscess was drained and temperature became normal and the redness, swelling and tenderness of the skin of the leg disappeared completely. The patient has remained well.

At that time, it did not occur to us to compare the reactivity of the skin over the involved area to injections of toxic filtrates. But as the uninvolved skin was very reactive, he was used to test several fractions so that he received fourteen endodermal injections. When tested two months after discharge, the skin of the involved area was less re-

active than uninvolved areas. This is in accord with subsequent experience in a number of cases.

In the chronic recurring cases the lesion usually involves the lower leg which becomes swollen tender and intensely red. The skin usually remains thin and blanches on pressure but here and there are outcroppings of a true erysipelatous aspect in which the skin itself is brawny, is not blanched by pressure and blebs form. The dorsum of the foot may or not be involved but often the entire foot may be swollen. There is usually femoral adenitis and general symptoms such as fever, chills, tachycardia, anorexia and headache. The recurrences which may appear after an interval of two weeks or six months are usually ushered in by the general symptoms of which the first sign may be fatiguability or sudden chill. The patients recognize immediately by these symptoms that another recurrence is imminent. They remain in bed for five days to two weeks and seem perfectly well between the attacks.

The following case history in abstract will illustrate this type of infection—

H. R. W., white man, aged 39 years, admitted September 24, 1927. Except for frequent colds up to four years ago when the sinuses were drained and tonsils enucleated, the patient enjoyed excellent health.

September 5, 1926 he suddenly experienced chill and high fever. His left leg became red, swollen and quite painful across the ankle to a line 7 cm. below the knee. A diagnosis of erysipelas was made. At operation was found to be a simple cellulitis. The patient recovered. He recovered the next year. In January, 1927, he had a recurrence of the same infection.

fection of the same leg which lasted for other two weeks. Since then there have been four more recurrences as follows:

Second attack January, 1927, two weeks duration.

Third attack April, 1927, eight days duration, right leg also involved.

Fourth attack June, 1927, two weeks duration.

Fifth attack July, 1927, three days duration.

Sixth attack August, 1927, two weeks duration.

He felt well between attacks and in spite of five attacks in eight months gained 13 pounds in weight.

September, 1927. The general physical examination revealed nothing abnormal. Laboratory tests added nothing of interest. Cultures of the nose and throat failed to demonstrate streptococci or any other predominating organisms.

Between the toes on both feet, however, an epidermophyton infection was discovered, identified microscopically but not cultivated.

To determine sensitivity to several of the streptococcus filtrates, he was tested September 29, 1927, by endodermal injections of C strain and B strain filtrates both on the leg and on the arm. He was positive to both the reactions were more marked on the legs. On October 1, immunization was started by gradually increasing doses of B filtrate subcutaneous. He was tested again to the toxic filtrates November 26 (one and a half months later) when it was found that he did not react to B filtrate (used in his immunization) but still remained markedly positive to C filtrate. The reaction was more marked on the arm than in the area of the leg which had been affected. The patient has gained 20 pounds and feels well. He has applied dusting powder to the toes after washing them in warm water and alcohol twice daily. The itching of the legs which previously had been severe enough to keep him awake, has disappeared.

Skin test with 1 cc. of 1:100 dilution of B strain of erysipelas was negative.

The control consisted of 0.1 cc of 1 to 100 tryptic broth			
Date	Area tested	Filtrate	Reaction
Sept 29	left arm	Filtrate B	++
		Filtrate C	++
	left leg	Filtrate B	+
		Filtrate C	++
			Control 0

Subcutaneous injection of increasing doses of B filtrate were made at five-day intervals from October 10 to November 21

Date	Area tested	Filtrate	Reaction	Control
Nov 26	left arm	Filtrate B	±	0
		Filtrate C	+++	
	left leg	Filtrate B	0	
		Filtrate C	+	

From November 26 to February 5, at five day intervals increasing doses of C filtrate were injected subcutaneously. Tests were made again on May 19, 1928. The skin of the arm and leg reacted to filtrate of strain C but not to filtrate B. The reactions were more intense on the arm than on the leg.

This patient has had no recurrence in 3 1/2 years.

Two points in this abstract form the basis of our present method of treating such patients.

1) The skin on the affected side when tested during the interval between attacks, reacted to a greater degree to the endermal injection of the streptococcus filtrate (so called strept-allergin) than the skin of the other leg, or of the arm. A course of injections of gradually increasing doses of the streptallergin was followed by the state of nonreactivity earlier in the affected area than in the other leg. Because of this fact it may be assumed that the skin over the involved area was in a state of hypersensitivity. The involved area has not been more reactive in but 15 of the 23 cases tested, but in every patient there was a marked reaction. The tentative hypothesis that the lesion is an allergic response is supported also by the fact that in no instance has it been possible to cultivate hemolytic streptococci from skin puncture. It has been shown by biopsy that a few organisms are pres-

ent (culture) yet they are sparsely scattered in small nests throughout the tissues.

2) The second point is the presence of a break in the skin between the toes on the affected side from which epidermophyta were seen in the scrapings. In some cases they have been cultivated. In every case there has been a fungus infection on one or both feet and when the lesion is visible on only one side it is invariably on the side on which the recurrent cellulitis appears.

In four cases hemolytic streptococci have been obtained from culture of the debris removed from the edge of the toe nails.

The plan of the treatment is as follows — The skin at symmetrical points on the legs is tested for sensitivity by the injection of 0.1 cc of 1-100 filtrate from 6 stock strains. The strain provoking the greatest reaction is used as the desensitizing agent. Increasing doses of 1-100 dilution are given at five day intervals usually doubling the dose each time. The process is then continued with 1-10 and finally with the undiluted filtrate. After 5 doses of 1 cc of the undiluted filtrate the areas are again tested and if the reaction zone measures over 1 cm at 24 hours the injections are continued with

the filtrates which provoke reaction

Inasmuch as it is probable that the fungus infections open the way for the entrance of the streptococci, efforts are directed toward the removal of this very resistant infection. The routine procedure is as follows—

Whitfield's ointment, which is a 5 per cent salicylic acid salve is reinforced by the addition of 1 per cent thymol iodide and applied each night. After cleansing with soap and water the next morning the skin between the toes and of the soles of the feet is wiped from 70 per cent alcohol and a 1 per cent solution of thymol iodide in 70 per cent alcohol is applied and allowed to dry. A dusting powder of the following composition is used—

Salicylic acid	5
Thymol iodide	1.
Boric acid	
Starch aa	50

and when the socks are changed at 5 P M the affected areas are cleaned as in the morning. Soiled socks are boiled as soon as possible after removal.

Among the 23 patients treated (of whom 3 are still under observation) there have been no recurrences. The longest period of observation is 3½ years. In two other cases of recurring lymphangitis following burns with extensive scarring the treatment seems to be little value.

The 23 patients studied have come from the several states: two from New York, two from Texas, one from California and the remainder from the South Atlantic States.

It is possible that the immunizing process is not necessary. Perhaps the care of the feet is the essential part and it is recommended that this be tried first.

The Historical Development of the Present Conception of Cardiac Conditions in Exophthalmic Goiter*

By A MORRIS GINSBERG, A B, M D, F A C P, *Kansas City, Missouri*

ALLOW your imagination to wander back five hundred years and picture a medieval castle upon a mountain top. Note how it stands majestically, a towering and commanding edifice. You might compare this castle to the thyroid gland, standing as it does at the top of human emotions and commanding its every act. It is then, and then only, that you are able to appreciate this small but "mighty" organ whose symptoms are expressed in practically every tissue in the body. The thyroid gland may be responsible for symptoms manifested in the skin, blood, bones, joints, muscles, the lymphatic glands, the nervous system, the gastrointestinal system, the genito-urinary system, the metabolic system, the endocrine system and, probably most conspicuously, in the cardiovascular system. It is, indeed, important to remember that these distant areas may first call the attention of the alert physician to pathology of the thyroid gland. All grades and variations of these referred symptoms are experienced and, I am sorry to say, it is not rare for even the mature doctor of note to miss the diagnosis. In other words, I desire to emphasize

the fact that we must remember that, although thyrotoxicosis is a localized disease of the thyroid gland, it has myriads of generalized symptoms which may be manifested anywhere from the head to the toes.

These distant symptoms may precede for months any enlargement of the thyroid gland and it is not unusual to encounter cases which *never* show any thyroid enlargement whatsoever.

Fate is a trickster and often barely misses making an individual immortal. Such was the case with the Bath physician, Caleb Hillier Parry,¹ who described exophthalmic goiter, as we know it today, fifty years before either Graves or von Basedow discovered the symptom complex. Osler often said that Parry should be given credit for having first clearly described hyperthyroidism. Not only did he describe this disease but he was the first to call attention to the symptoms referable to the heart. This was in 1786. I shall quote his first case:

"There is one malady which I have in five cases seen coincident with what appeared to be enlargement of the heart, and which, so far as I know, has not been noticed, in that connection, by medical writers. The malady to which I allude is enlargement of the thyroid gland."

*Received for publication April 25, 1931

"The first case of this coincidence which I witnessed was that of Grace B., a married woman, aged thirty-seven, in the month of August, 1785. Six years before this period she caught cold in lying-in, and for a month suffered under a very acute rheumatic fever, subsequently to which, she became subject to more or less of palpitation of the heart, very much augmented by bodily exercise and gradually increasing in force and frequency till my attendance, when it was so vehement, that each systole of the heart shook the whole thorax. Her pulse was 156 per minute, very full and hard, alike in both wrists irregular as to strength, and intermitting, at least once in six beats. She had no cough, tendency to fainting, or blueness of the skin, but had twice or thrice been seized in the night with a sense of constriction and difficulty of breathing, which was attended with a spitting of a small quantity of blood. She described herself also as having frequent and violent stitches of pain about the lower part of the sternum.

"About three months after lying-in, while she was suckling her child, a lump of about the size of a walnut was perceived on the right side of her neck. This continued to enlarge till the period of my attendance, when it occupied both sides of her neck, so as to have reached an enormous size, projecting forwards before the margin of the lower jaw. The part swelled was the thyroid gland. The carotid arteries on each side were greatly distended, the eyes were

morning and often threw up fluid tinged with bile.

"She nursed for a year the child of her first lying-in, during which time she did not menstruate. Subsequently to that period she had five times miscarried, and for the last four months her menses had been irregular as to intervals and defective in quantity and colour. Bowels usually lax and more especially so for the last three weeks. It was directed that six ounces of blood be taken from her arm and that she should take twice a day, a pill consisting of dried Squill and quicksilver triturated with Manna, of each, one grain.

"The bleeding almost immediately relieved the dyspnea and stitches across the sternum. But the edematous swellings were increased and the urine did not exceed half a pint in twenty-four hours. She had been purged seven or eight times each day. Her pulse was 114, full and hard, and never more than six strokes without intermission. This was the state of symptoms on the sixteenth of August. The bleeding was ordered to be repeated and the pills to be continued.

"I did not again see her till the twenty-fifth when she had taken eight of the pills, which did not affect the mouth, but had produced seven or eight watery stools daily. The urine, however, did not amount to three ounces in the twenty-four hours and was very high colored and extremely turbid on standing, with a copious sediment. Her drink was about a quart in the day. Each systole of the heart shook the whole trunk.

Graves⁴ described the syndrome. In 1840, Von Basedow⁵ called attention to the triad of goiter, cardiovascular symptoms and exophthalmus. In 1863, Potain⁶ contributed a clinical discussion to the subject. The same year Trousseau⁷ used tincture of iodine instead of tincture of digitalis by mistake on a toxic thyroid heart and, when he discovered his error and stopped the iodine, the heart condition was made worse. In 1878, Rose⁸ first emphasized the importance of the heart in sudden deaths of patients with goiter. He felt it was due to a mechanical factor. In 1879, Lockridge⁹ wrote about this disease and wished to name it "Cardiac Exophthalmic Goiter." Others, at this time, reported cases which they believed to be very much influenced by nervous factors. In 1896, Mobius¹⁰ emphasized the importance of tachycardia, palpitation, forceful beating of the heart and the arrhythmia in these cases of thyroid disease and stated that exophthalmic patients "suffer and die through their hearts, practically always is the condition of the heart important." In 1899, Kraus¹¹ was the first to suggest the toxic theory of exophthalmic goiter. It was Kocher¹² who said that he believed the surgeon should be guided by the cardiac condition in choosing the time and the extent of the operation and that there were probably no cases of exophthalmic goiter in which cardiac symptoms were completely wanting.

As we come down to the present time, we find the pendulum is swinging to the opposite side. We hear authorities such as Willius, Boothby and Wilson^{13,14} say that "the most out-

standing fact is the infrequency in both exophthalmic goiter and adenoma with hyperthyroidism of symptoms indicating cardiac disease." Hurxthal¹⁵ states that there is "no evidence that thyrotoxicosis injures normal healthy hearts because there is very little, if any, evidence of damage in cases under forty." Too, Lahey and Hamilton¹⁶⁻¹⁹ write that "young individuals with previously undamaged hearts suffer no cardiac changes, no matter how intense the toxicity."

How are we to reconcile our clinical findings with these recent statements?

Let us for a moment turn to the pathological and experimental data at hand. Wilson²⁰ in eighteen cases of hyperthyroidism found that the myocardium showed "swollen fibers with indistinct striations and well-marked lipid changes." Only five patients were under forty. He further states "that in patients with long-continued pronounced hyperthyroidism the myocardium shows more-advanced fat-changes than are present in the myocardium of individuals of the same age without hyperthyroidism."

Fahr²¹ described two patients who died of heart failure following partial thyroidectomy. He found an interstitial myocarditis with an accumulation of round cells between the muscle fibers and in the neighborhood of small vessels, as well as degenerative changes, such as fragmentation and destruction of muscular fibers. He further described three other patients with hyperthyroidism who also showed at autopsy, small round cell infiltration, fatty degeneration and hyaline focal necrosis.

Goodpasture²² had two cases with auricular fibrillation who died of myocardial exhaustion. One showed a focal necrosis of the myocardium and the other an extensive necrosis. However, these two patients had pathology other than the hyperthyroidism which could account for the myocardial necrosis.

More recently, Thomas²³ reports a case of exophthalmic goiter with cardiac decompensation, who died on the third day. He found a slight increase in connective tissue about a few blood vessels, a slight infiltration of polynuclears and mononuclears between the strands of fibers. The cause of death of the patient, however, was a coronary thrombus. He reports an exophthalmic goiter patient with cardiac decompensation and auricular fibrillation of more than a year's duration, who made such a complete recovery that he felt that severe intoxication certainly need not produce permanent cardiac damage.

Hashimoto²⁴ examined two hearts from exophthalmic patients and found "lymphocytic infiltration between muscle fiber or around blood vessels."

These reported cases are too few to permit us to form a definite opinion.

Goodpasture²² fed rabbits thyroid extract and thyroxin and found "slight but definite lesions in the myocardium, notably perivascular necrosis or fibrosis in the wall of the right ventricle, focal necrosis or fibrosis in the papillary muscles of the left ventricle and moderate to gross focal necrosis in the myocardium of the left ventricle." When the thyroid extract was fed to dogs, the results were similar, but the lesions were less pronounced. He also found that the lesions were more pronounced in the myocardium of the left ventricle than in the right ventricle.

to the conclusion that "hearts overstimulated by disease of the thyroid and laboring in a condition bordering on exhaustion were in a state of greater susceptibility to injury by toxic substances, such as may have resulted from a relatively mild terminal infection which, under other circumstances, might not have injured the myocardium." This conclusion is certainly well-worth remembering. Tonsillectomy or pulling of the teeth, in such a patient, may bring disastrous results.

Hashimoto²⁴ produced experimental myocarditis in animals with toxic doses of dried thyroid substances and found interstitial tissue lesions not unlike the Aschoff nodules in acute rheumatic fever and when the lymphocytic infiltration was increased it caused disintegration and destruction of muscle fibers. The hearts of these animals showed enlargement.

Farranti²⁵ found in the hearts of thyroid-fed cats and rabbits swollen muscle fibers with few nuclei and no transverse striations. Iscovesco²⁷ found that repeated injections of thyroid extract produced, in rabbits, hypertrophy of the heart. Other organs such as suprarenals, ovaries, uterus, spleen and kidneys shared in this enlargement. Hoskins,²⁸ Herring,²⁹ Hewitt³⁰ and others³¹ obtained similar results, namely: hypertrophy of the heart and hypertrophy of the other organs. Experiments by Simonds and Brandes³² who fed desiccated thyroid to dogs resulted in further proof that there is actual hypertrophy of the heart.

Certainly the experimental fed heart can be injured.

Does the heart have more susceptibility to injury by toxic substances?

Sane³³ report an increased minute volume output of the heart in thyrotoxicosis and this increase is proportional to the increase in metabolism. The systolic output per beat of the heart decreases after thyroidectomy. Fullerton and Harrop³⁴ found a parallelism between the increase in basal metabolism and cardiac output per minute. Rabinowitch and Bazin³⁵ are the only ones who did not find an increased cardiac output in thyrotoxicosis. Robinson³⁶ studied a case of thyrotoxicosis and found that the cardiac output was actually increased to a greater degree than the oxygen consumption of the body. This means that, in this disease, there is a constant extra load imposed on the heart. In this particular case, Robinson found after thyroidectomy that the minute output fell from 10,000 cc to 3,890 cc, while the metabolism fell from plus 58 to plus one. This gives us some idea as to the great amount of work the heart does in thyrotoxicosis. Burwell and his coworkers³⁷ found a definite increase in cardiac output in thyrotoxicosis.

What are the subjective symptoms referable to the cardiovascular system in thyrotoxicosis? At the outset, let me state that there is little difference in the cardiac disturbances, between exophthalmic goiter and the adenoma with secondary hyperthyroidism. It must be remembered, however, that exophthalmic goiter is usually found in much younger individuals than is adenoma with hyperthyroidism. For that reason, we must expect physiologic changes in the cardiovascular tree in these older patients

with adenoma and secondary hyperthyroidism.

Probably the first symptom of which these patients complain is palpitation or being conscious of their heart action, usually brought on by mental or physical exertion of a mild nature. The sensation of pounding in the chest will naturally unnerve an already highly-nervous patient. Sometimes, there are attacks of palpitation of a paroxysmal nature and it is then that we suspect an irregularity. Soon these patients notice undue breathlessness or fatigue on the least exertion. It is not long, thereafter, that this dyspnea becomes more marked. The patient flushes freely and spasmodically on account of the great lability of the vasomotor system. A common complaint is the throbbing in the neck and a sense of tightness or constriction of it. Quite often distress over the precordia or a fullness in the chest may send the patient hurriedly to the doctor. This distress or fullness, even called pain by some, is not severe. There is no radiation of this discomfort and usually it is designated as being in the region of the apex or toward the anterior axillary line.

Upon *inspection*, we see increased carotid pulsation and flushing of the face and neck. The skin of the face, neck and upper chest has a salmon hue, hyperemic and somewhat pigmented. The peripheral vessels, too, may show increased pulsation. Capillary pulsations are frequently noted. Looking at the precordia, we note a forceful apex impulse which gradually increases its power and, as time goes on, the apex beat becomes diffuse and can be noted moving downward and outward.

Graves⁴ described the syndrome. In 1840, Von Basedow⁵ called attention to the triad of goiter, cardiovascular symptoms and exophthalmus. In 1863, Potain⁶ contributed a clinical discussion to the subject. The same year Trousseau⁷ used tincture of iodine instead of tincture of digitalis by mistake on a toxic thyroid heart and, when he discovered his error and stopped the iodine, the heart condition was made worse. In 1878, Rose⁸ first emphasized the importance of the heart in sudden deaths of patients with goiter. He felt it was due to a mechanical factor. In 1879, Lockridge⁹ wrote about this disease and wished to name it "Cardiac Exophthalmic Goiter." Others, at this time, reported cases which they believed to be very much influenced by nervous factors. In 1896, Mobius¹⁰ emphasized the importance of tachycardia, palpitation, forceful beating of the heart and the arrhythmia in these cases of thyroid disease and stated that exophthalmic patients "suffer and die through their hearts, practically always is the condition of the heart important." In 1899, Kraus¹¹ was the first to suggest the toxic theory of exophthalmic goiter. It was Kocher¹² who said that he believed the surgeon should be guided by the cardiac condition in choosing the time and the extent of the operation and that there were probably no cases of exophthalmic goiter in which cardiac symptoms were completely wanting.

As we come down to the present time, we find the pendulum is swinging to the opposite side. We hear authorities such as Willius, Boothby and Wilson^{13,14} say that "the most out-

standing fact is the infrequency in both exophthalmic goiter and adenoma with hyperthyroidism of symptoms indicating cardiac disease." Hurxthal¹⁵ states that there is "no evidence that thyrotoxicosis injures normal healthy hearts because there is very little, if any, evidence of damage in cases under forty." Too, Lahey and Hamilton¹⁶⁻¹⁹ write that "young individuals with previously undamaged hearts suffer no cardiac changes, no matter how intense the toxicity."

How are we to reconcile our clinical findings with these recent statements?

Let us for a moment turn to the pathological and experimental data at hand. Wilson²⁰ in eighteen cases of hyperthyroidism found that the myocardium showed "swollen fibers with indistinct striations and well-marked lipid changes." Only five patients were under forty. He further states "that in patients with long-continued pronounced hyperthyroidism the myocardium shows more-advanced fat-changes than are present in the myocardium of individuals of the same age without hyperthyroidism."

Fahr²¹ described two patients who died of heart failure following partial thyroidectomy. He found an interstitial myocarditis with an accumulation of round cells between the muscle fibers and in the neighborhood of small vessels, as well as degenerative changes, such as fragmentation and destruction of muscular fibers. He further described three other patients with hyperthyroidism who also showed at autopsy, small round cell infiltration, fatty degeneration and hyaline focal necrosis.

Goodpasture²² had two cases with auricular fibrillation who died of myocardial exhaustion. One showed a focal necrosis of the myocardium and the other an extensive necrosis. However, these two patients had pathology other than the hyperthyroidism which could account for the myocardial necrosis.

More recently, Thomas²³ reports a case of exophthalmic goiter with cardiac decompensation, who died on the third day. He found a slight increase in connective tissue about a few blood vessels, a slight infiltration of polynuclears and mononuclears between the strands of fibers. The cause of death of the patient, however, was a coronary thrombus. He reports an exophthalmic goiter patient with cardiac decompensation and auricular fibrillation of more than a year's duration, who made such a complete recovery that he felt that severe intoxication certainly need not produce permanent cardiac damage.

Hashimoto²⁴ examined two hearts from exophthalmic patients and found "lymphocytic infiltration between muscle fiber or around blood vessels."

These reported cases are too few to permit us to form a definite opinion.

Goodpasture²² fed rabbits thyroid extract and thyroxin and found "slight but definite lesions in the myocardium, notably perivascular necrosis or fibrosis in the wall of the right ventricle, and necrosis or fibrosis in the papillary muscle of the left ventricle and in the interventricular septum. In the myocardium there was a small focal necrosis." We have not been able to find any other reports of myocardial necrosis in the thyroid disease of animals.

to the conclusion that "hearts overstimulated by disease of the thyroid and laboring in a condition bordering on exhaustion were in a state of greater susceptibility to injury by toxic substances, such as may have resulted from a relatively mild terminal infection which, under other circumstances, might not have injured the myocardium." This conclusion is certainly well-worth remembering. Tonsillectomy or pulling of the teeth, in such a patient, may bring disastrous results.

Hashimoto²⁴ produced experimental myocarditis in animals with toxic doses of dried thyroid substances and found interstitial tissue lesions not unlike the Aschoff nodules in acute rheumatic fever and when the lymphocytic infiltration was increased it caused disintegration and destruction of muscle fibers. The hearts of these animals showed enlargement.

Farranti²⁵ found in the hearts of thyroid-fed cats and rabbits swollen muscle fibers with few nuclei and no transverse striations. Iscove-co²⁷ found that repeated injections of thyroid extract produced, in rabbits, hypertrophy of the heart. Other organs such as suprarenals, ovaries, uterus, spleen and kidneys shared in this enlargement. Hoskins,²⁸ Herring,²⁹ Hewitt³⁰ and others³¹ obtained similar results, namely: hypertrophy of the heart and hypertrophy of the other organs. Experiments by Simonds and Brandes³² who fed desiccated thyroid to dogs resulted in further proof that there is actual hypertrophy of the heart.

Certainly the experimental feeding of thyroid can be proved.

Does the heart have more work to do in the hyperthyroid state? Metabolism

Sane³³ report an increased minute volume output of the heart in thyrotoxicosis and this increase is proportional to the increase in metabolism. The systolic output per beat of the heart decreases after thyroidectomy. Fullerton and Harrop³⁴ found a parallelism between the increase in basal metabolism and cardiac output per minute. Rabinowitch and Bazin³⁵ are the only ones who did not find an increased cardiac output in thyrotoxicosis. Robinson³⁶ studied a case of thyrotoxicosis and found that the cardiac output was actually increased to a greater degree than the oxygen consumption of the body. This means that, in this disease, there is a constant extra load imposed on the heart. In this particular case, Robinson found after thyroidectomy that the minute output fell from 10,000 cc to 3,890 cc, while the metabolism fell from plus 58 to plus one. This gives us some idea as to the great amount of work the heart does in thyrotoxicosis. Burwell and his coworkers³⁷ found a definite increase in cardiac output in thyrotoxicosis.

What are the subjective symptoms referable to the cardiovascular system in thyrotoxicosis? At the outset, let me state that there is little difference in the cardiac disturbances, between exophthalmic goiter and the adenoma with secondary hyperthyroidism. It must be remembered, however, that exophthalmic goiter is usually found in much younger individuals than is adenoma with hyperthyroidism. For that reason, we must expect physiologic changes in the cardiovascular tree in these older patients

with adenoma and secondary hyperthyroidism.

Probably the first symptom of which these patients complain is palpitation or being conscious of their heart action, usually brought on by mental or physical exertion of a mild nature. The sensation of pounding in the chest will naturally unnerve an already highly-nervous patient. Sometimes, there are attacks of palpitation of a paroxysmal nature and it is then that we suspect an irregularity. Soon these patients notice undue breathlessness or fatigue on the least exertion. It is not long, thereafter, that this dyspnea becomes more marked. The patient flushes freely and spasmodically on account of the great lability of the vasomotor system. A common complaint is the throbbing in the neck and a sense of tightness or constriction of it. Quite often distress over the precordia or a fullness in the chest may send the patient hurriedly to the doctor. This distress or fullness, even called pain by some, is not severe. There is no radiation of this discomfort and usually it is designated as being in the region of the apex or toward the anterior axillary line.

Upon *inspection*, we see increased carotid pulsation and flushing of the face and neck. The skin of the face, neck and upper chest has a salmon hue, hyperemic and somewhat pigmented. The peripheral vessels, too, may show increased pulsation. Capillary pulsations are frequently noted. Looking at the precordia, we note a forceful apex impulse which gradually increases its power and, as time goes on, the apex beat becomes diffuse and can be noted moving downward and outward.

Goodpasture²² had two cases with auricular fibrillation who died of myocardial exhaustion. One showed a focal necrosis of the myocardium and the other an extensive necrosis. However, these two patients had pathology other than the hyperthyroidism which could account for the myocardial necrosis.

More recently, Thomas²³ reports a case of exophthalmic goiter with cardiac decompensation, who died on the third day. He found a slight increase in connective tissue about a few blood vessels, a slight infiltration of polynuclears and mononuclears between the strands of fibers. The cause of death of the patient, however, was a coronary thrombus. He reports an exophthalmic goiter patient with cardiac decompensation and auricular fibrillation of more than a year's duration, who made such a complete recovery that he felt that severe intoxication certainly need not produce permanent cardiac damage.

Hashimoto²⁴ examined two hearts from exophthalmic patients and found "lymphocytic infiltration between muscle fibers or around blood vessels".

These reported cases are too few to permit us to form a definite opinion.

Goodpasture²⁵ fed rabbits thyroid extract and thyroxin and found "slight but definite lesions in the myocardium, notably perivascular necrosis or fibrosis in the wall of the right ventricle, focal necrosis or fibrosis in the papillary muscles of the left ventricle and more rarely scattered small focal necrosis within the myocardium elsewhere". "With chloroform inhalation, these animals showed widespread myocardial necrosis." He, therefore, came

to the conclusion that "hearts overstimulated by disease of the thyroid and laboring in a condition bordering on exhaustion were in a state of greater susceptibility to injury by toxic substances, such as may have resulted from a relatively mild terminal infection which, under other circumstances, might not have injured the myocardium". This conclusion is certainly well-worth remembering. Tonsillectomy or pulling of the teeth, in such a patient, may bring disastrous results.

Hashimoto²⁴ produced experimental myocarditis in animals with toxic doses of dried thyroid substances and found interstitial tissue lesions not unlike the Aschoff nodules in acute rheumatic fever and when the lymphocytic infiltration was increased it caused disintegration and destruction of muscle fibers. The hearts of these animals showed enlargement.

Farranti²⁶ found in the hearts of thyroid-fed cats and rabbits swollen muscle fibers with few nuclei and no transverse striations. Iscovesco²⁷ found that repeated injections of thyroid extract produced, in rabbits, hypertrophy of the heart. Other organs, such as suprarenals, ovaries, uterus, spleen and kidneys shared in this enlargement. Hoskins,²⁸ Herring,²⁹ Hewitt³⁰ and others³¹ obtained similar results, namely hypertrophy of the heart and hypertrophy of the other organs. Experiments by Simonds and Brandes³² who fed dessicated thyroid to dogs resulted in further proof that there is an actual hypertrophy of the heart.

Certainly these experimental findings cannot be ignored.

Does the heart have more work in thyrotoxicosis? Davies, Meakins and

Sane³³ report an increased minute volume output of the heart in thyrotoxicosis and this increase is proportional to the increase in metabolism. The systolic output per beat of the heart decreases after thyroidectomy. Fullerton and Harrop³⁴ found a parallelism between the increase in basal metabolism and cardiac output per minute. Rabinowitch and Bazin³⁵ are the only ones who did not find an increased cardiac output in thyrotoxicosis. Robinson³⁶ studied a case of thyrotoxicosis and found that the cardiac output was actually increased to a greater degree than the oxygen consumption of the body. This means that, in this disease, there is a constant extra load imposed on the heart. In this particular case, Robinson found after thyroidectomy that the minute output fell from 10,000 cc to 3,890 cc, while the metabolism fell from plus 58 to plus one. This gives us some idea as to the great amount of work the heart does in thyrotoxicosis. Burwell and his coworkers³⁷ found a definite increase in cardiac output in thyrotoxicosis.

What are the subjective symptoms referable to the cardiovascular system in thyrotoxicosis? At the outset, let me state that there is little difference in the cardiac disturbances, between exophthalmic goiter and the adenoma with secondary hyperthyroidism. It must be remembered, however, that exophthalmic goiter is usually found in much younger individuals than is adenoma with hyperthyroidism. For that reason, we must expect physiologic changes in the cardiovascular tree in these older patients

with adenoma and secondary hyperthyroidism.

Probably the first symptom of which these patients complain is palpitation or being conscious of their heart action, usually brought on by mental or physical exertion of a mild nature. The sensation of pounding in the chest will naturally unnerve an already highly-nervous patient. Sometimes, there are attacks of palpitation of a paroxysmal nature and it is then that we suspect an irregularity. Soon these patients notice undue breathlessness or fatigue on the least exertion. It is not long, thereafter, that this dyspnea becomes more marked. The patient flushes freely and spasmodically on account of the great lability of the vasomotor system. A common complaint is the throbbing in the neck and a sense of tightness or constriction of it. Quite often distress over the precordia or a fullness in the chest may send the patient hurriedly to the doctor. This distress or fullness, even called pain by some, is not severe. There is no radiation of this discomfort and usually it is designated as being in the region of the apex or toward the anterior axillary line.

Upon *inspection*, we see increased carotid pulsation and flushing of the face and neck. The skin of the face, neck and upper chest has a salmon hue, hyperemic and somewhat pigmented. The peripheral vessels, too, may show increased pulsation. Capillary pulsations are frequently noted. Looking at the precordia, we note a forceful apex impulse which gradually increases its power and, as time goes on, the apex beat becomes diffuse and can be noted moving downward and outward.

Palpation reveals a rapid pulse, soft and, at times, dicrotic, it might even be somewhat of a water-hammer pulse. Tachycardia is always present. The rate varies tremendously from day to day. Elliot³⁸ tersely puts it "A patient showing a persistent tachycardia, temporary or permanent, should always be thought of at least, as a possible thyroid." Too, Gmelin³⁹ called attention to certain characteristics of the tachycardia, that it is constant with bed rest at night; that it is not influenced by drugs or narcotics, and that it disappears promptly after operation.

This increased rate is not evidence of heart disease but is evidence of a response to the increased demands made upon the heart by the increased metabolism. The precordia reveals to palpitation, a forceful apex beat, first localized and then diffuse and moving to the left and downward as the disease progresses. Quite often we are led to believe that we are feeling a systolic or even a presystolic thrill. At the pulmonic area, we may feel a distinct shock due to the violent closure of the pulmonic valve.

When the heart is *percussed*, we get a definite increase of the relative dullness downward and outward; later, the right border-dullness is increased. Ofttimes the base shows an increased dullness.

Auscultation reveals a whistling sound, a bruit over the carotids and their branches particularly over the thyroid arteries. A so-called "pistol-shot" may be heard over the brachials and femorals. The sounds of the heart are loud, especially so is the first sound. Often two types of murmurs

are heard, both are systolic in time and blowing in quality. One is best heard at the third left intercostal space and is localized. The second is best heard at the apex and has a variable transmission. It is thought that the first is probably due to changes in the blood-flow, while the apical murmur is probably due to functional regurgitation at the mitral valve due to dilatation of the left ventricle. Improvement or cure of the hyperthyroidism results in the disappearance of these. It must be remembered that in hyperthyroidism, we never hear diastolic murmurs unless there is an associated heart lesion and this, of course, might be present.

Willius and Boothby, in a series of toxic thyroid patients found, for exophthalmic goiter, a blood pressure average of 147 systolic and 73 diastolic and a pulse rate of 123, while in the adenoma with secondary hyperthyroidism, the systolic average was 153 and the diastolic was 83 and the pulse rate 110. It is seen that in the toxic adenoma patient, the systolic blood pressure is elevated considerably more than it is in exophthalmic goiter and it differs also from exophthalmic goiter in that the diastolic is also increased. "It is rare to find in exophthalmic goiter a diastolic over 90, while in toxic adenomas, it is not unusual to find readings over 100." Bed rest and activity, either physical or mental, will obviously influence blood pressure readings.

Harris⁴⁰ noted a relationship between pulse rate and pulse pressure in exophthalmic goiter. In tachycardia due to bacterial toxins, acting on the heart muscle; in the tachycardia of

other forms of myocardial disease, in the tachycardia of cardiac neurasthenia and in the tachycardia of heart failure, the pulse pressure is usually diminished and Harris believes that it is only in exophthalmic goiter that there is both an increase in pulse rate and, at the same time, a high pulse pressure. It is interesting to note that blood pressure readings in auricular fibrillation are the same as in normal rhythmic cardiac action.

It is an old fact now that in thyrotoxicosis, there is an increased basal metabolism. The resulting rapid pulse rate and heightened pulse pressure is a physiologic response to bring about an increased rate of circulation. Means and Aub⁴¹ noted a close parallelism between pulse rate and metabolism in about sixty per cent of cases, while in the remainder, there was only a certain amount of parallelism. They concluded that, in exophthalmic goiter patients, just as Benedict and Murchauser⁴² concluded in normal cases, there is a relationship between heart rate and metabolism in different individuals, but in a single individual, the resting rate is a good index of the patient's progress. Sturgis and Tompkins⁴³ feel that a pulse rate at complete rest below 90 is seldom and that one below 80 is rarely associated with an increase in metabolism. This, of course, is of practical importance.

Boothby and Willius⁴⁴ in basal metabolism tests on patients suffering with primary cardiac disease, find that the level is slightly elevated in comparison to that of the normal but that in decompensated cases, there is a definite increase in the metabolism. They feel this is due to actual increase in muscu-

lar work required in labored respirations and also due to the subjective sensation of distress with resultant nervousness. DuBois⁴⁵ and Lev and Hamburger⁴⁶ report similar findings of increased metabolism in patients, suffering from primary heart disease and decompensation.

German Sée,⁴⁷ in 1878, emphasized the fact that the association of irregularity of the heart with exophthalmic goiter had frequently been overlooked. This is probably what we today call auricular fibrillation. Bamberger⁴⁸ as late as 1919 collected only twenty-two cases of paroxysmal tachycardia in the literature. He mentions that irregularity of the heart was present and this, of course, would suggest paroxysmal auricular fibrillation. In 1918, Krumbhaar⁴⁹ reported fifty-one cases of toxic goiter studied with the electrocardiograph. He found four cases with sinus arrhythmia, three with ventricular extra-systoles, three with auricular fibrillation, one with auricular flutter and two with delayed conductivity. In 1922, Hamilton⁵⁰ found eighteen cases of auricular fibrillation in 200 cases of hyperthyroidism. He says that "very few cases of hyperthyroidism over fifty fail to show auricular fibrillation." Willius, Boothby and Wilson^{13, 14} in 377 patients with thyrotoxicosis found constant auricular fibrillation in eight per cent and transient auricular fibrillation in nine per cent of the exophthalmic goiters, while in toxic adenomas, they found ten per cent in each group. They emphasized that the *duration* of the increased metabolic rate is most important in regard to development of auricular fibrillation. Phillips and Ander-

son⁵¹ conclude that auricular fibrillation is the most common cardiac irregularity associated with hyperthyroidism and that it will usually disappear, if thyroidectomy is performed before the heart has been permanently injured. It is interesting to note that Stewart and Crawford⁵² found experimentally on dogs that the heart is less efficient in the propulsion of blood, during irregular tachycardia than during the normal slower rhythm.

Willius, Boothby and Wilson found fifteen per cent of cases to have extrasystoles, which they feel have no significance in thyroid disorder. Paroxysmal tachycardia was not a common disorder in thyroid disease, occurring in about one per cent of cases.

Hoffman,⁵³ in 1914, was the first to describe high T-waves in the electrocardiograph tracings of patients, suffering with exophthalmic goiter. Krumbhaar⁴⁹ described an "unusually prominent T-wave in most cases of toxic goiter which, in about one-half of the cases, was markedly and persistently diminished after operation." Furthermore, he states that a diphasic or inverted T-wave, especially in Leads I and II, offers an unfavorable prognosis. Willius, Boothby and Wilson do not comment on the height of the T-wave except to call attention to the infrequency (one per cent) of inversion of the T-wave. This infrequency is due to the fact that degenerative changes in the myocardium are not common in hyperthyroidism. Hamburger⁵⁴ and his co-workers report several cases of their series as having a high T-wave which showed a definite lowering of the height when the thyroid was removed. Previous rest with-

out iodine has no effect but with iodine a lowering of the T-wave in most cases is noted. They, however, found no uniformity in the increased height and concluded that it had little, if any, relation to pulse rate. It is well to remember in this connection that Rothberger and Winterberg⁵⁵ found in patients, having a marked accelerator tone, a high T-wave.

The association of hyperthyroidism and angina pectoris is rare. Lev and Hamburger⁵⁶ report six cases; Sturgis⁵⁸ reports one case. Hurxthal¹⁵ found two cases with angina pectoris out of 500 cases of cardiac failure with hyperthyroidism. Haines and Kepler⁵⁷ remark that it is easy to overlook angina pectoris in the presence of severe hyperthyroidism, or mild hyperthyroidism in a patient with angina pectoris. A heart having a coronary supply which is sufficient under ordinary circumstances, may be inadequate to meet the demands placed upon it by the added work of the heart produced by hyperthyroidism and hence, the patient suffers pain. An interesting case, which recently came to my attention, was that of a patient with myxedema of, at least, ten years standing, with a minus metabolism of forty-three, who had a bundle-branch block and who suffered definite attacks of angina pectoris when she received over one and one-half grains of thyroid extract.

Sturgis⁵⁸ reports a similar case of myxedema with associated heart disease in whom attacks of angina pectoris were produced when more than one-half gram of thyroid extract was taken.

Recently, we have read many articles regarding cases of so-called "masked hyperthyroidism." It was Charcot,⁵⁹ in 1885, under the heading "Maladie de Basedow formes frustes," who called attention to a group of cases in which one of the triad of characteristic symptoms of exophthalmic goiter was missing. Chvostek,⁶⁰ in 1887, considered these formes-frustes cases as "symptom poor" cases in contrast to the well-developed typical cases. Levine and Sturgis,⁶¹ in 1924, under the title "Hyperthyroidism Masked as Heart Disease," reported five cases. Priest⁶², in 1926, reported three cases of hyperthyroidism, simulating primary heart disease. In 1928, Tucker⁶³ reported three cases of hyperthyroidism without visible or palpable goiter. Hamburger and Lev⁶⁴ report five cases, under the title of "Masked Hyperthyroidism." Freund and Cooksey⁶⁵ also report five cases of thyrotoxicosis, without visible or palpable thyroid. These patients are middle-aged individuals, who do not present the classical picture of hyperthyroidism, but who show a group of symptoms which, if analyzed, will place them in the hyperthyroid field. They have a staring expression of the eyes, an increased warmth, redness or pigmentation of the skin, increased restlessness and unexplained loss of weight, and come to the doctor with a complaint in one of the main systems, quite often cardiovascular. They have a persistent increased metabolism and under iodine medication or thyroidectomy, they improve or get completely well. This group must be kept in mind, as its ranks are increasing due to the added stress and strain

which men and women over forty-five are now experiencing.

All of us have seen cases of hyperthyroidism which give no history of previous heart involvement and still have symptoms of heart failure. Hurxthal¹⁵ studied 500 cases and came to the conclusion that the average age of congestive heart failure was above forty with a large percentage showing previous cardiovascular disease. He feels that "thyrotoxicosis has a specific excitatory effect on the heart and that this, more than the demands for increased work, produces failure in a heart weakened by the degenerative processes of age." In his opinion, the most significant causes of congestive heart failure in hyperthyroidism are age and its accompanying cardiovascular changes, the specific heart drive, auricular fibrillation, and the duration and intensity of thyroid activity. Andrus⁶⁶ feels that when congestive heart failure appears under forty that there must be "a pre-existent rheumatic or more rarely a syphilitic heart disease." If you will review your own cases, you will be struck by the fact that the majority of these congestive heart-failure patients were older individuals, who, for many years, had adenomatous thyroids with secondary hyperthyroidism. These patients usually give a history of many exacerbations and remissions.

A review of this kind would certainly lack completeness, if I did not discuss a condition more prevalent than even thyrotoxicosis. I mean the syndrome of neuro-circulatory asthenia or "effort syndrome" as it affects the cardiovascular tree and which might even be mistaken for a toxic thyroid

heart You can well imagine the difficulty in diagnosis when such a patient has an associated enlarged thyroid.

Addis and Kerr⁶⁷ examined many recruits, during the war, and found these embryonic soldiers were complaining of increased pulse rate, tremor, and of cold, moist hands which became cyanosed when dependent. They even complained of precordial pain with dyspnea and palpitation on moderate exertion, dizziness, flushing and fainting This condition was found both in patients who had normal-sized thyroids and those who had enlarged thyroids Addis and Kerr felt that the thyroid had no etiologic relationship to the nervous picture Plummer, though, feels that these patients with neurocirculatory asthenia are more prone to thyroid enlargement than are normal individuals

Remember, in this condition, that this tachycardia disappears with rest and sleep Dell' Acque and Aschner⁶⁸ noted in hyperthyroidism that the average pulse rate increased 4.82 upon changing from a reclining to a standing posture, while in neurotic patients, it was five times as great, namely, 25.3 This might be a good diagnostic point. Peabody and his co-workers⁶⁹ found that the basal metabolism was normal

in soldiers with so-called "irritable" hearts and furthermore they were impressed with the fact that these patients showed a marked tachycardia, easily provoked by mental or physical strain, which disappeared when they were allowed to lie down for a short period

SUMMARY

Parry should be given credit for first describing thyrotoxicosis and especially so its cardiac manifestations The fact that cardiac complications, in young people, are infrequent; the fact that severe intoxications give no clinical picture of decompensation in previously undamaged hearts, the fact that after complete relief, by thyroidectomy in previously undamaged hearts, there is a complete return of normal cardiac findings, all tend to uphold the opinion that hyperthyroidism does not cause permanent myocardial changes As the so-called "irritable heart" in neurocirculatory asthenia approaches in symptomatology the heart in thyrotoxicosis, we must not lose sight of the variations in tone of the vagus and sympathetic nerves, which might play a cardinal rôle In a practical consideration of this topic, it is well ever to keep in mind that hyperthyroidism does cause marked subjective heart symptoms

BIBLIOGRAPHY

- ¹PARRY, CALEB HILLIER Collections from the unpublished Medical Writings of the late Caleb Hillier Parry, London, 1825, II, 111
- ²TRAJANI, G. Concerning a peculiar tumor in the anterior part of the neck. Collection of Surgical Observations and Experiments, Rome, 1802, III, 277
- ³WOLFF, Beiträge zur Pathologie des Herzens, der Luftröhre und der

- Gehirns. Jahrbücher der philosophisch Medizinischen Gesellschaft zu Würzburg, I, 104 and II, 108
- ⁴GRAVES, R. J. Exophthalmic Goiter. London Med. Surg. Jr., 1835, VII, 510
- ⁵VON BASEDOW. Exophthalmus durch Hyper-trophie des Zellgewebes der Schilddrüse. Casus. Wochenschr. für die Heilk., 1849, 107 and 229

- ^cPOTAIN Quoted from Chvostek, F Morbus Basedow und die Hyperthyreosen, Berlin, 1917, 372
- ⁷TROUSSFAU, A Clinical lectures translated by Bazire, London, 1868, New Sydenham Society, 1, 587
- ⁸ROSE Quoted from Chvostek, F Morbus Basedow und die Hyperthyreosen, Berlin, 1917, 372
- ⁹LOCKRIDGE, J E Graves' disease or cardiac exophthalmic goiter, Am Practitioner, 1879, xix, 287
- ¹⁰MOBIUS, P J Die Basedow'sche Krankheit, Nothnagel's System, 1896, xxii, 1, Holder, Alfred, Specielle Pathologie und Therapie Wien
- ¹¹KRAUS, F Über Kropfherz, Beziehungen zwischen Struma und Morb Basedowii, Wien klin Wchnschr, 1899, xii, 416
- ¹²KOCHER, A In Kraus and Brugsch Specielle Pathologie und Therapie, 1919, ix, 751
- ¹³WILLIUS, F A, BOOTHBY, WM, and WILSON, L B The behavior of the heart in exophthalmic goiter and adenomatous goiter, Tr Assoc Am Phys, 1923, xxxviii, 137
- ¹⁴WILLIUS, FRANK A, BOOTHBY, WALTER M, and WILSON, L B Cardiovascular response in 377 patients Med Clinics of N A, 1923, vii, 189
- ¹⁵HURXTHAL, L M Heart failure and hyperthyroidism, The Am Heart Jr, 1928, iv, 103
- ¹⁶LAHEY, F H, and HAMILTON, B E Thyrocardiacs their diagnostic difficulties, their surgical treatment Surg, Gyn and Obst, 1924, xxxix, 10
- ¹⁷LAHEY, F H Hyperthyroidism associated with cardiac disorders, Surg, Gyn and Obst, 1930, l, 39
- ¹⁸LAHEY, F H Deductions of 6700 goiter operations, New Eng Jr Med, 1929, cc, 909
- ¹⁹LAHEY, FRANK H End results in thyrocardiacs Ann of Surg, 1929, xc, 750
- ²⁰WILSON, L D Note on the pathology of hearts from cases described by Doctors Wilhus and Boothby, Trans Assoc Am Phys, 1923, xxxviii, 144
- ²¹FAHR Histologische Befunde an Kropfherzen, Centralbl f allg Path u path Anat, 1916, xxvii, 1
- ²²GOODPASTURE, ERNEST W Myocardial necrosis in hyperthyroidism, Jr Am Med Assoc, 1921, lxxvi, 1545
- ²³THOMAS, HENRY M, JR Thyroid heart, a transitory condition, Bull Johns Hopkins Hosp, 1930, xlvii, 1
- ²⁴HASHIMOTO, H The heart in experimental hyperthyroidism with special reference to its histology, Endocrinology, 1921, v, 579
- ²⁵GOODPASTURE, ERNEST W The influence of thyroid products on the production of myocardial necrosis, Jr Exp Med, 1921, xxxiv, 407
- ²⁶FARRANTI, R Hyperthyroidism its experimental production in animals, Brit Med Jr, 1913, ii, 1363
- ²⁷ISCOVESCO, H Action physiologique, en particulier sur la croissance d'un lquoide, extrait de la thyroide Compt rend Soc de Biol, 1913, lxxvii, 361
- ²⁸HOSKINS, E R The growth of the body and organs of the albino rat affected by feeding various ductless glands J Exp Zool, 1916, xxi, 295
- ²⁹HERRING, P T The action of thyroid upon the growth of the body and organs of the white rat Quart Jr Exper Phys, 1917, xi, 231
- ³⁰HEWITT, J A The effect of administration of small amounts of thyroid gland on the size and weight of certain organs in the male white rat, Quart Jr Exper Phys, 1920, xii, 347
- ³¹CAMERON, A T, and CARMICHAEL, J Comparative effects of thyroid and iodide feeding on growth in white rats and in rabbits, Jr Biol Chem, 1920, xlv, 69
- ³²SIMONDS, J P, and BRANDES, W W The size of the heart in experimental hyperthyroidism, Arch Int Med, 1930, xlv, 503
- ³³DAVIS, H WHITRIDGE, MEAKINS, JONATHAN, and SANDS, JANE The influence of circulatory disturbances on the gaseous exchange of the blood V The blood gases and circulatory rate in hyperthyroidism, Heart, 1924, xi, 299

- ³⁴FULLERTON, CHARLES W, and HARROP, GEORGE A, JR The cardiac output in hyperthyroidism, Bull Johns Hopkins Hosp, 1930, xlv, 203
- ³⁵RABINOWITZ, I M, and BAZIN, ELEANOR V. The output of the heart per beat in hyperthyroidism, Arch Int. Med, 1926, xxxviii, 566
- ³⁶ROBINSON, G C The measurement of the cardiac output in man and its variations, Jr Am Med Assoc, 1926, lxxxvii, 314
- ³⁷BURWELL, C SYDNEY; SMITH, W CARTER, and NEIGHBORS, DEWITT The output of the heart in thyrotoxicosis with report of a case of thyrotoxicosis combined with primary anemia, Am. Jr Med. Sc, 1929, clxxxviii, 157
- ³⁸ELLIOTT, CHARLES A Cardiac disturbance with hyperthyroidism, Proc Inter-State Post-Graduate Med Assembly of N Am, 1927, 286
- ³⁹GMELIN, E Zur Klinik des Kropfherzens, Arch f klin Chir, 1926, cxliii, 726
- ⁴⁰HARRIS, I Pulse pressure in exophthalmic goiter, Brit Med Jr., 1923, 1, 630
- ⁴¹MEANS, J H., and AUB, J C. The basal metabolism in exophthalmic goiter, Arch Int. Med, 1919, xxiv, 645
- ⁴²BENEDICT, F G, and MURCHHAUSER, H Energy transformations during horizontal walking, Carnegie Institution of Washington, Publication 231
- ⁴³STURGIS, CYRUS C, and TOMPKINS, EDNA H. A study of the correlation of the basal metabolism and pulse rate in patients with hyperthyroidism, Arch Int Med, 1920, xxvi, 467
- ⁴⁴BOOTHBY, W. M., and WILLIUS, F A. The basal metabolic rate in cases of primary cardiac disease, Med Clinics, N Am., 1925, viii, 1171.
- ⁴⁵DUBOIS, E F Basal metabolism in health and disease 1924, Lea and Febiger, Philadelphia, 306
- ⁴⁶LEV, MORRIS, and HAMBURGER, W W. Basal metabolism in organic heart disease, Am Heart Jr 1925, i, 240
- ⁴⁷SIL, GRIMAIN Symptomes de la Maladie de Basedow's La France Méd 1878 xxv, (8)
- ⁴⁸BAMBERGER Paroxysmal Tachykardie bei Morbus Basedowii, Deutsch Med Wchnschr, 1918, xxxv, 1403
- ⁴⁹KRUMBHAAR, E B Electrocardiographic observation in toxic goiter, Am J Med Sc., 1918, clv, 175
- ⁵⁰HAMILTON, B E Clinical notes on hearts in hyperthyroidism, Boston Med and Surg Jr, 1922, clxxxvi, 216
- ⁵¹PHILLIPS, JOHN, and ANDERSON, J P Cardiac disturbances in goiter, Jr Am Med Assoc., 1927, lxxxix, 1380
- ⁵²STEWART, HAROLD J, and CRAWFORD, J HAMILTON The effect of tachycardia on the blood flow in dogs, Jr of Clin Investigation, 1926, iii, 449
- ⁵³HOFFMAN, A. Die Electrocardiographie Wiesbaden, 1914, 108
- ⁵⁴HAMBURGER, W. M., LEV, MORRIS W., PRIEST, WALTER S, and HOWARD, HELEN C The heart in thyroid disease, Arch Int Med, 1929, xliii, 35
- ⁵⁵ROTHBERGER and WINTERBERG Personal study
- ⁵⁶LEV, MORRIS, and HAMBURGER, WALTER The association of angina pectoris and hyperthyroidism Am Heart Jr, 1928, iii, 672
- ⁵⁷HAINES, SAMUEL F, and KEPLER, EDWIN J. Angina pectoris associated with exophthalmic goiter and hyperfunctioning adenomatous goiter, Med Clinics of N Am, May, 1930
- ⁵⁸STURGIS, CYRUS C Angina pectoris as a complicating factor in myxedema and exophthalmic goiter, Boston Med and Surg Jr, 1926, cxcv, 351
- ⁵⁹CHARCOT, T M. Maladie de Basedow formes frustes, nouveau signe physique; traitement per l' electricite Gaz. d. hôp. 1885, xiii, 15
- ⁶⁰CHVOSTEK, F. Morbus Basedowii, "Formes Frustes" Wien med Presse, 1887.
- ⁶¹LEVINE, S A, and STURGIS, C. C: Hyperthyroidism masked as heart disease, Boston Med and Surg Jr, 1924, cxc, 233
- ⁶²PRIEST, W. S. Cases of hyperthyroidism simulating primary heart disease, Med Clinics N. Am., 1926, ix, 1337
- ⁶³LUCKER, J P. Hyperthyroidism without visible or palpable goiter, Am Jr. Med Sc., 1928, clxxxi, 504

- ⁶¹HAMBURGER, WALTER W, and LEV, MORRIS, W Masked hyperthyroidism, Jr Am Med Assoc, 1930, xciv, 2050
- ⁶²FREUND, HUGO A, and COOKSEY, WARREN B Thyrotoxicosis in elderly persons without signs of goiter, Jr Am Med Assoc, 1930,xciv, 1891
- ⁶³ANDRUS, COWLES Heart failure with hyperthyroidism N Y State Jr Med, 1929, xxix, 661
- ⁶⁴ADDIS, T, and KERR, W T The relative frequency in recruits with and without thyroid enlargement of certain signs and symptoms which occur in neurocirculatory asthenia, Arch Int Med, 1919, xliii, 316
- ⁶⁵DRILL' ACQUER, G, and ASCHNER, B Influence of posture on tachycardia caused by nervous disorders or by hyperthyroidism, Klin Wchnsch, Berlin, 1930, ix, 397 Abs Jr Am Med Assoc, 1930, xciv, 1635
- ⁶⁶PEABODY, F W, WEARN, J T, and TOMPKINS, E H The basal metabolism in cases of "irritable heart" of soldiers, Med Clinics N Am, (Sept) 1918, ii, 507

Editorials

THE PROGRAM FOR THE GENERAL SESSIONS OF THE SIXTEENTH ANNUAL CLINICAL SESSION IN SAN FRANCISCO

In the week of April 4, 1932, will occur one of the great medical meetings of the year. The Annual Session of the College has become a focal point for those interested in the medical, as contrasted with the surgical, interests of our profession.

That the College is meeting a need in medicine on this continent has been attested by its remarkable growth in numbers and in influence during its relatively short existence, and particularly during the period of less than a decade following its reorganization. The College stands today as representative of those practitioners who are concerned with both the science and the art in medicine, as the American College of Surgeons is a meeting ground for those concerned with the surgical specialties. The College has not attempted, nor has it manifested at any time a desire, to invade the fields so well cultivated by the American Medical Association, The American Hospital Association, The Association of Medical Colleges and other associations formed for promotion of their own various interests. The primary purposes of the College are the encouragement and preservation of high standards, the dissemination of knowledge within its field and the elevation of the historic and esthetic ground in which medicine, as

one of the learned professions, grows. There is no desire to set the members of the College apart from other medical men; but there is clearly shown a desire to stimulate all men in medicine to the level of professional, ethical and cultural achievement at which fellowship in the College is possible.

Each session of the College has reflected the purposes and ideals thus briefly stated. The San Francisco Session will be the first to be held beyond the Mississippi. While the United States census has shown in recent decades only a slow movement of the center of population westward along the thirty-ninth parallel, located now in southwestern Indiana, there has been a remarkable development, not only in population, but also in power, in influence and in culture along the entire Pacific Coast. Here a people from the same ethnic sources and with, in general, the same cultural and political purposes as found in our population eastward has accumulated. But this people has a genius of its own. There is a freshness in its point of view, an exuberance in its spirit, and a capacity for building great industries and noble institutions that set it somewhat apart, due, no doubt, in good measure to its sea and valley and mountain. San Francisco occupies a position near the center of the great

empire and this makes it a fitting seat for the first meeting of the College to be held within its bounds

Two great medical schools form the nucleus of an important medical center. The medical school of the University of California, with the Hooper Foundation for Medical Research, and the Stanford University Medical School are known the world over. These institutions, with their laboratories and hospitals, together with all other medical facilities around and about the Bay of San Francisco, have been placed at the disposal of the College for the week of the meeting. Each morning, on Tuesday, Wednesday, Thursday and Friday, clinics and demonstrations will be held in which the advanced work in these institutions will be exemplified. As is customary, each member of the College will be given an opportunity, long in advance of the meeting, to choose the places he desires to visit and the men and subjects he wishes to hear. This is arranged from the office of the Executive Secretary of the College and the early disposal of this matter, which might otherwise be confusing, lends order to this part of the program. The arrangement of the laboratory and clinical portion of the program is in the hands of Dr. Wm. J. Kerr, Professor of Medicine in the University of California, who is general chairman for the Session. This will be the second meeting in which the President of the College has been responsible for the program of the general sessions, attended by all fellows, associates and guests, and in which all the formal papers and addresses are presented. There will be five after-

noon and two evening sessions of this character. On Monday the short introductory program of welcome will be followed by scientific papers. On Monday evening a program of extraordinary interest will be presented. On both Tuesday afternoon and evening the scientific sessions will continue, while on Wednesday, Thursday and Friday, only the afternoons will be thus occupied, Wednesday and Thursday evenings being given over to the convocation and the banquet.

For the seven afternoon and evening sessions set aside for the presentation of scientific and practical matters before the entire group, a program of outstanding merit with some unique features is being arranged. This seemed to your President to be an opportunity for the exposition of the best medicine on the Pacific Coast. Men deemed capable of sound and scientific presentation have been invited to take part and their response has been very gratifying. The members of the College will thus have an opportunity to see and hear a remarkable group not so commonly seen and heard when the programs are given farther east. This opportunity of contact with men about whose work we know and yet with whom contact has not been as frequent as desired will be a feature of great value and interest.

While there is an unusual number of new names on our program, both from the coast states and from the country at large, the outstanding names in medicine will be well represented. This is not the time nor place to detail names and subjects but it may be said that a program of wide

range and interest has been arranged. Final selection of many offerings is still to be made. Experience has shown that not more than about fifty papers and addresses can be well presented in the allotted time, giving fifteen to twenty minutes to each presentation, with an occasional extension of time when the interest of the subject requires it.

Even to suggest the wide range of subjects offered would be difficult, but the appearance of certain trends in modern medicine makes this attempt worth while. There will be the study of the physics and physiology of arteriosclerosis and hypertension by a master. Pulmonary arteriosclerosis and the congenitally narrowed aorta have a place. The onset of decompensation of the heart in elderly patients, a follow-up study of hypertension, and an experimental and clinical study of the effect of hypothyroidism upon the heart with two studies of an extensive material, one on cardiovascular syphilis and one on the electrocardiograms, will give valuable contributions to our knowledge of the heart and blood vessels. The lungs and bronchi are studied from several angles. Atelectasis and tuberculosis, the treatment of cavities, some observations on pulmonary emphysema and the rôle of bacteria in asthma will be among the subjects of unusual interest. The liver will receive attention with subjects ranging from the effect of the administration of glucose and insulin on the glycogen content, to an unusual study of the histology of the liver in chloroma. As to the kidneys, the new methods of control and of study of the function of the organ will be presented. Edema of the

disease and a study of the relationship of nephritis and nephrosis.

The practical applications of recent discoveries in the field of gastro-intestinal physiology, the absorption of sugar from the intestinal tract, the clinical aspects of gastric secretions, and the elements of error in diagnosis in jaundiced patients are to be discussed. On the subject of the adrenal glands, there will be presentations of unusual significance from both the experimental and clinical standpoints. The biological and clinical importance of ovary-stimulating substances will be brought out. There will be a study of calcium metabolism and diseases of the parathyroid gland. Recent studies on the chemical pathology of epilepsy and on its treatment appear. We will learn something more of the mechanism of edema formation in disease. There is a study of leukopenia, on the action of benzol, roentgen rays and radium on the blood and blood-forming organs, on the relation of paranasal sinus infection to disease elsewhere, on the clinical significance of the atrophic tongue; and on the experimental basis for vaccine treatment of chronic arthritis with a summary of results of treatment. There will be studies on the chemotherapy of amebiasis, together with a consideration of human amebiasis.

While there will be many groupings of papers on allied subjects, symposia do not constitute an outstanding feature of the program. One symposium, however, will make up for the lack of many others. Recent years have seen an almost unbelievable advance in our knowledge of the involuntary nervous system. Not only have the autonomic

been able to construct a fairly comprehensible picture of it but the physiologists have delved deeply into its function in many species of animals and very recently have added greatly to our knowledge of hormonal control. Pituitary hormone, adrenalin and acetyl cholin have been subjected to such intensive study that their actions are becoming quite thoroughly known. Much has been learned recently of the sympathetic control of the kidneys and of blood pressure, of the peripheral vessels, of the gastrointestinal tract and of the urinary bladder. Even as this knowledge has been developing, surgery has been making use of it. It, therefore, seems that a symposium on the involuntary nervous system, which would bring together the anatomist, the physiologist, clinicians in medicine, and surgeons, would be of the most profound interest. If you think of the names of the men you would most wish to hear on these subjects, you will be likely to find them on the program when it is finally announced. An outstanding anatomist in this field, and the two greatest physiologists in this country, are on the program for this symposium.

The history of medicine has been given a place on previous programs, notably that of the Minneapolis meeting, and approval of this feature by the Fellows has been very general. At this time of unrest and uncertainty, affecting medicine as it does all other walks of life, an address on medicine in Utopia will be particularly appropriate. Many books on Utopia have been written and the relation of the ideas about medicine in that happy land

will have an immediate interest. There is a lively story on medicine on the Pacific Coast and it is hoped that this can be made available.

Many other items of interest are on the program but this will suffice to show that the program of the General Session of the San Francisco meeting promises to reach the high standards set in recent years. The opportunity of securing low rates of travel to the coast, the extension of time customary for travelers to this region, the opportunity either preceding or following the meeting for vacations in the land of sunshine and flowers, should make the San Francisco Session one of the most attractive we have ever held. Subsequent issues of the *ANNALS* will give all the details of arrangement and of the program. It is to be hoped that all Fellows will give a ready response to the efforts of our California hosts.

S M W

THE SASKATCHEWAN EXPERIMENT

In Saskatchewan, and to a less extent in Manitoba, there is in operation a "municipal doctor" system which is intended to solve the problem of obtaining good medical care for the residents of certain rural communities. The character of this system with its policies and procedures is the subject of the eleventh publication of the Committee on the Cost of Medical Care, by C. Rufus Rorem. The rural municipality, composed of nine townships, is entirely apart as a unit of government from such cities, towns or villages as may be situated within its area. Each

rural municipality is a unit for administrative purposes, including the levying of taxes. In Manitoba there are three, and in Saskatchewan there are twenty municipalities which employ full-time physicians and levy taxes to pay for this service. Twelve others make grants of \$1,500 or less as inducements to physicians to practice in their communities, and as remuneration for services as public health officers and for the care of indigent persons. The median salary of the twenty full-time municipal doctors in Saskatchewan is \$4,000. Each serves an average population of about 1,800, receives from 1,000 to 1,500 office calls annually, and makes from 300 to 500 visits to the homes of patients. Notwithstanding the full-time status, opportunity is provided in nearly all cases for the municipal physician to earn additional income from special services. In some instances he is directed to make nominal charges for specified services. An interesting example of these is a fee for the "initial" house visit in any illness. Apparently the object of this is to discourage house calls for minor conditions which could be properly treated at the office. Most of the municipalities levy taxes upon the basis of the value of farm lands and the municipal physician levy usually amounts to between \$7.50 and \$10.00 per family. Arrangement is usually made by which transients and residents not eligible to the service may be treated upon a fee basis. The doctors themselves say that while they do more work they also receive a larger net income than could be earned by private practice in the same areas, partly because there are no "bad debts." Certain advan-

tages and disadvantages of this entire system, which is fundamentally merely contract practice, are obvious. Opposition has come largely from non-resident landowners, from well-to-do farmers with small families, and from those living close to the doctor's office. Independent physicians in towns included within the areas of the rural municipalities using this system and in adjacent communities recognize that the presence of municipal physicians has had unfavorable economic effects upon their practice; and private physicians in Saskatchewan on the whole express disapproval of the system, although they admit that in certain rural areas it may be the only way to assure the continued presence of a medical practitioner. This, as well as other modifications of the time-honored relationship between physician and patient in private practice, should receive careful attention and study. Whether his initial reaction is one of strong disapproval or not, the medical man of today can ill afford to be indifferent to such tentative schemes for altering medical economics. Rather should he study and weigh each of them that he may be prepared to exercise a constructive directing influence if occasion arises. If modifications are ever found necessary, they should originate within the medical profession itself, and not be foisted upon it. They should represent the best constructive thought of which the medical mind is capable. Only through such active participation in the economics of public health can the medical profession hope to uphold those high standards of practice which are absolutely essential.

ACCIDENTAL INJURIES AND OCCUPATIONAL DISEASES

In a recent decision, the Tennessee Supreme Court (*Morrison vs Tennessee Consolidated Coal Co*, 39 S W (2d) 272, decided June 10, 1931) holds that there is no recourse under the workmen's compensation act for a disease, occupational or otherwise, unless that disease naturally results from an accidental injury. Further "an injury to be regarded as an accidental injury under the compensation act, must be an injury unforeseen, unexpected, and fortuitous. An element of unexpected casualty must be present." Likewise, the origin or inception of the disease must be assignable to a determinate or single occurrence identified in space or time, it was pointed out. This decision is seemingly in accord with the general usage of the terms in the statutes and probably rightly interprets the spirit of the earlier phase of the movement to insure compensation for occupational injuries. However, it should attract attention to the fact that there is a general tendency to apply the principle of compensation more broadly than the original intent of the law. In addition to those occupational in-

juries which are accidental in the sense defined in the decision to which reference has been made, many now consider it both proper and desirable that compensation should be paid for those injuries which grow out of the long continued operation of the causes of occupational disease. Here the situation is somewhat different. In many instances, instead of the element of the unforeseen, unexpected and fortuitous casualty being present, the worker has entered upon his employment in full knowledge that a hazard existed and has elected, although it may be under the stress of necessity, to expose himself to that hazard. One must feel in accord with the desire to give such workers compensation, especially when they have not been made aware of the hazards existing. It would seem, however, that cooperative insurance with the cost apportioned between the employer and the employed more justly meets the needs of this group. At least, it is highly desirable that statutes providing compensation for occupational injuries and occupational diseases be so framed as to discriminate between the various classes of those entitled to the benefits which are provided.

Abstracts

The Etiology of Gall Stones I Chemical Factors By RUDOLPH SCHOENHEIMER and LEO HRDINA (Proc Soc Exp Biol and Med, 1931, xxviii, 944-945)

The problem of gall stone formation is the problem of the precipitation of cholesterol out of the bile. The question has been investigated as to whether the ability of bile to hold cholesterol in solution might be due to some one or all of the bile acids. It was found that the precipitation of bile acids from human bile by ferric chloride, by lead acetate, or by any other means produces a simultaneous precipitation of cholesterol. The complexes of bile acids and cholesterol are readily soluble in water and may be purified without lessening the cholesterol content. Large amounts of these complexes have been isolated from human bile in which it appears that all or nearly all of the cholesterol is thus bound. In dog or ox bile, on the contrary, most of the bile acids are in combination with fatty acids rather than cholesterol. This explains the complete absence of cholesterol-containing gall stones in these animals. As for man, this investigation shows that whenever the organism by any pathological processes brings about a significant lowering of the bile acids in the gall bladder in relation to the amount of cholesterol in it precipitation of cholesterol is bound to occur.

The Etiology of Gall Stones II Role of the Gall Bladder By EDMUND ANDREWS, RUDOLPH SCHOENHEIMER and LEO HRDINA (Proc Soc Exp Biol and Med, 1931, xxviii, 945-946)

Under normal conditions the gall bladder concentrates bile, in its concentrating effect upon the bile salts, to absorb water rapidly; while bile salts and cholesterol if they are absorbed at all, are absorbed at an equal rate. It is not possible to store any longer than a few hours bile salts to hold

the cholesterol in solution. In a series of experiments in which the cystic duct was ligated, leading to infection of the gall bladder, with added traumatic insult, the action was diametrically opposite in respect to differential absorption. In every case an increase in the concentration of cholesterol was found, averaging + 29 per cent, and a lessening in the concentration of the bile salts, averaging - 28 per cent, was found. The ratio of bile salts over cholesterol was 97 for normals and 59 for sixteen experiments. This change is sufficiently marked to cause precipitation of cholesterol if continued for any length of time. Apparently the gall bladder mucosa has great absorptive power for bile salts if diseased.

The Etiology of Gall Stones III Bile Salt-Cholesterol Ratio in Human Gall Stone Cases By EDMUND ANDREWS, RUDOLPH SCHOENHEIMER and LEO HRDINA (Proc Soc Exp Biol and Med, 1931, xxviii, 947-948)

The two preceding studies having suggested that cholesterol stones are found in the human gall bladder because there are not enough bile salts present to hold the cholesterol in solution, one would expect to find in human gall bladders with cholesterol stones a lesser quantity of bile salts. Results of analyses confirm this expectation. In a group of operated cases the bile salt-cholesterol ratio was found to average 3.4, and in the mixed bladder bile from 30 examples of cholelithiasis found post-mortem this ratio was 0.6. The control series of Newman on normal human gall bladders gave a bile acid-cholesterol ratio of from 10 to 24 and Hammarsten found ratios of 10 and 30 respectively in two cases of sudden accidental death. These figures add further proof to the theory that cholesterol stones are due to a fault, differential absorption of bile acid and cholesterol by the abnormal gall bladder mucosa.

Lead Poisoning in Brass and Bronze Foundries By FRANK G. PEDLEY, M.D., D.P.H. (The Canadian Med Assoc Jr, 1931, xxv, 299-303)

Lead poisoning is an important hazard in certain types of bronze foundries. Bronze is essentially an alloy of copper and tin, and brass an alloy of copper and zinc. However, this distinction is not always observed in naming alloys. Lead is frequently added to both, sometimes to improve them, sometimes to cheapen them. In railroad bronzes, such as bearings, the antifrictional qualities of lead make it a valuable constituent and it may be present in amounts as high as 20 per cent. The hazard arises in part through the volatilization of lead at the temperature necessary to insure the melting of the copper constituent in the preparation of the alloy and during the subsequent pouring of the molten alloy, and, in part, from the subsequent grinding and polishing of the castings. Of 38 men engaged in the founding of high lead bronze, 24 were found to be suffering from acute lead poisoning, nine others showed definite evidence of lead absorption, and only five showed no evidence of plumbism. Three brass polishers who succeeded each other on the same emery wheel became poisoned with lead. Blood smears were examined from 26 men engaged in polishing low lead brass and bronze (less than six per cent lead). Five of these showed stippled cells in a number well in excess of 200 per million red cells. It is the belief of the author that lead plays an important part in the disease pictures variously diagnosed as brass poisoning, bronze poisoning, and copper poisoning.

The Relation of Heredity to the Occurrence of Spontaneous Leukemia, Pseudoleukemia, Lymphosarcoma and Allied Diseases in Mice, Preliminary Report By MAUD SLYE (Am Jr of Cancer, 1931, xv, 1361-1385)

The familial occurrence of human leukemia and of the related lymphatic diseases has been noted repeatedly. While the data in each individual report are few, they are

all in agreement in indicating that in man the leukemic diseases have an hereditary basis and tend to run in families, and, further, that they tend to occur in cancer strains. Dr Slye found 975 examples of the leukemic diseases in the first 50,000 mice autopsied by her. The division between the sexes was practically equal. All instances of leukemia, pseudoleukemia, and lymphosarcoma were in families carrying other forms of malignancy. All occurrences of these diseases have been in a limited number of strains of mice. Whole races of mice of other derivation, but living for many generations under identical environmental conditions, have been entirely free from these conditions. The difficulty in certain recognition and differentiation of members of this group of diseases by histopathological methods is fully recognized, yet the results obtained furnish both negative and positive evidence for the assumption that the tendency to these diseases and the absence of these diseases are both subject to the control of heredity. Likewise since the leukemic diseases were found to occur in cancer strains only, there is strong evidence in support of the view that the leukemias, pseudoleukemias, and lymphosarcomas are members of the neoplastic group.

Tumor Immunity By THOMAS LUMSDEN, M.D. (The Am Jr of Cancer, 1931, vi, 563-640)

From extensive experimentation with several strains of transplantable tumors, Lumsden believes that it may be safely concluded that anti-malignant-cell bodies, lethal to cancer cells but harmless to normal tissue cells, can be produced. When an implanted tumor already established in the body is gradually destroyed by injecting antiserum or formalin into it, active immunity against the tumor is induced by a mechanism which may be called autovaccination. It has still to be learned whether similar effects can be obtained with spontaneous tumors, in which the relationship between host tissue and invading tissue may be quite different.

Reviews

The Pathology of Internal Diseases. By WILLIAM BOYD, M D, M R C P, Ed, Dipl Psych, F R S C, Professor of Pathology in the University of Manitoba, Pathologist to the Winnipeg General Hospital, Winnipeg, Canada xvi + 888 pages 298 illustrations Lea and Febiger, Philadelphia, 1931 Price, \$10.00

This is a companion volume to the author's *Surgical Pathology*, with only a minimum of unavoidable overlapping between the two. It aims to present the pathology of those diseases which are found in the medical wards of a teaching hospital and to relate their signs and symptoms to deviations from the normal in morphology and function. In this it succeeds admirably. Naturally no one pair of book covers can enclose all of the material which the subject foreshadows. Certain gaps must occur. Certain infectious diseases, diseases of special importance in the tropics, and others in regard to which no clear cut pathological picture has been established, have been intentionally excluded. In many respects the choice of material has been made with great skill. Throughout, special attention is given to presenting the newer knowledge in pathology, not that which is so new as to be ephemeral, but the very things which, although well established, the internist will find entirely wanting or very sketchily given in his older books. This is a pathology text of intriguing interest for the upper class student and the practitioner whose interest is not with the fundamental tissue lesions as such, but with the pathological processes of individual disease conditions. The reviewer finds himself very often in sympathetic accord with the point of view of the author in various matters that are not accepted by all. For instance, the fact that rheumatism in its various forms and gradations is a fairly well unified series is

clearly emphasized, so-called acute massive collapse of the lung is not considered a condition *suu generis* but merely a special manifestation of pulmonary atelectasis, and toxic adenomas of the thyroid and exophthalmic goiter are grouped under the heading of Graves' disease. However, it is not because of general agreement with its subject matter that the writer commends this work. It is rather because he realizes its splendid usefulness as a text in special pathology, as collateral reading in internal medicine, and as a reference book for the practitioner who wishes to keep up with the advances in pathology.

Deep X-Ray Therapy in Malignant Diseases. A Report of an Investigation Carried Out from 1924-1929 under the Direction of the St Bartholomew's Hospital Cancer Research Committee. By WALTER M. LEVITT, M B, D M R E, Medical Officer in charge of the Radiotherapeutic Research Department. With an introduction by SIR THOMAS HORDER, Bart, K C V O, M D, F R C P, Chairman of the Cancer Research Committee. 128 pages. John Murray, London, 1930. Price, 10 s 6 d, net.

This report gives the technical methods employed and the results obtained during the several years that the St Bartholomew's Cancer Research Committee (formerly the Radiotherapeutic Research Committee) has been actively engaged in the treatment of malignant disease by irradiation. Two main types of therapeutic technic were developed: (1) intensive single-dose technic in which the entire dosage is applied in one, or at the most in two or three days, and (2) intensive split-dose technic in which the dose is applied in several fractions at intervals of approximately 24 hours over a period of several days. The

number of fractions varies from 6 to 30. In 85 cases radium was used in addition to x-rays. So different are the results obtained in carcinoma of various regions that mass statistics are without meaning, and when split up into the necessary groups, the total number of cases in each is not large enough to be impressive. However, a certain degree of encouragement is afforded. Of 43 cases of inoperable carcinoma of the breast, 6 were still living at the time of report without signs of cancer present. In three of these, three or more years had elapsed since treatment. Thirteen of 60 cases of malignant disease of the uterus, chiefly carcinoma of the cervix, were reported alive without evidence of growth present. This was true also of 27 out of 170 cases of malignancy of the upper air passages. In the portion of this group suffering from carcinoma of the tonsil, the results were uniformly poor. Twenty-six cases of malignancy of the rectum were treated in the period under review, and of these only one was without evidence of the disease. In about 29 per cent of all cases treated, x-rays failed to have even a palliative effect, and in a further 22 per cent only minor degrees of improvement were observed, or improvement was of but short duration. In view of the statistical results, the conclusions stated in this report seem somewhat too sweeping, as being true of but a limited proportion of the cases. One must remember, however, that these patients were considered inoperable, and any salvage of human life or even temporary return to a state of economic independence, is something gained.

Resistance to Infectious Diseases. An Exposition of the Biological Phenomena Underlying the Occurrence of Infection and the Recovery of the Animal Body from Infectious Disease, with a Consideration of the Principles Underlying Specific Diagnosis and Therapeutic Measures. By HANS ZINSSER, M.D., Professor of Bacteriology and Immunity, Medical School, Harvard University, formerly Professor of Bacteriology at the College

of Physicians and Surgeons, Columbia University, and Bacteriologist to the Presbyterian Hospital, New York, formerly Professor of Bacteriology and Immunity, Stanford University, California. Fourth edition, completely revised and reset. xviii + 651 pages. The MacMillan Company, New York, 1931. Price, \$7.00.

Under this new title appears the fourth edition of Zinsser's *Infection and Resistance*. Advances which have been made in the eight years since the third edition came out have produced profound modifications in the theories of immunology and consequently in their application to methods of diagnosis and therapy. Many chapters have required rewriting in order to introduce new material and to eliminate that which has been discarded. The first section of the book, 486 pages, deals with fundamental conceptions and theories, while the second section discusses the problems of immunology as applied to individual infectious diseases. While the first portion of this book is indispensable to the teacher and laboratory worker, the second section will be of interest and value to the practitioner. Here are found full discussions of immunity in syphilis and tuberculosis, and of the applied principles of immunization in scarlet fever, pneumonia, typhoid and paratyphoid fever, meningitis, rabies, plague, cholera, anthrax, influenza, small pox and various other infectious diseases. This book can be heartily recommended to those who seek a comprehensive and authoritative text on immunology. Numerous bibliographic references, arranged as footnotes, give the sources of material other than that by the author. It is unfortunate that many of these references lack the page number, a very important aid after journals have been bound.

Food Allergy. Its Manifestations, Diagnosis and Treatment with a General Discussion of Branchial Asthma. By ALFRED H. ROWE, M.S., M.D., Lecturer in Medicine in the University of California Medical School, San Francisco, Calif., Chief of the Clinic for Allergic Diseases of the Alameda County Health Center, Oakland,

Calif., etc xi + 442 pages 1931, Lea and Febiger, Philadelphia Price, \$5.00 net

Forty-three per cent of 400 unselected individuals were found to give a family history of allergy, and a personal history of allergy occurred in thirty-five per cent of this group. In general, statistics show a probable food allergy in upward of thirty per cent of all persons. In the monograph under review the author treats this important subject in an extremely complete manner. The many diverse characteristics and manifestations of food allergy are described as they affect the gastro-intestinal system or result in bronchial asthma, eczema, urticaria or angioneurotic edema. Diseases less commonly related to allergy in diagnosis such as migraine, neuralgia, arthritis, bladder allergy, etc., are also considered. The frequency of negative skin reactions is emphasized and the method of "elimination diets" which was devised by the author is fully set forth as applied to both diagnosis and treatment. All internists will be interested in the section on the allergic aspects of drug sensitizations. This monograph is admirable in its completeness, in its scientific approach and in the reserve with which a subject has been handled, which might easily have led a specialist to make extravagant and unsupported generalizations. An extensive bibliography is provided.

Recent Advances in Cardiology By C. F. JERRARD FARR, M.A., M.D. (Oxon), F.R.C.P. (Lond.), Junior Physician, King's College Hospital, Physician, Woolwich Memorial Hospital, Sometime Radcliffe Travelling Fellow, University College, Oxford and C. W. CURTIS B.Sc., M.C., M.B. (Oxon), M.R.C.P. (Lond.); Physician Harrogate Infirmary. Second edition xi + 353 pages 10 plates and 62 text-figures. P. Blakiston's Son & Co., Inc., Philadelphia, 1931. Price, \$3.50.

This is the second edition of the Cardiology series of the *Recent Advances* series. It is a well written and comprehensive treatise on the subject of cardiology.

Certain sections have been entirely rewritten in this edition. Much attention is given to electrocardiographic findings throughout, and one chapter is devoted entirely to this method of examination. To the reviewer the presentation of myocardial syphilis seems entirely inadequate, for only the extremely active diffuse form is considered. The final chapter on the interpretation of certain misleading physical signs and symptoms which may be encountered even in those with presumably healthy hearts is especially important in connection with routine physical examinations. For the practitioner this will prove an extremely useful manual.

Lane Lectures on Pharmacology By WALTHFR. STRAUB M.D., Ph.D. (lic.). Professor of Pharmacology, University of Munich. (Stanford University Publications, University Series, Medical Sciences, Volume III, Number 1) 88 pages, 9 text-figures. Stanford University Press, Stanford University, California, 1931. Price, postpaid, paper \$1.00, cloth, \$1.50.

Professor Straub chose as subjects for his six Lane Lectures, delivered in San Francisco in April, 1929, the following: Intoxicating Drugs, Ways to Ideal Anesthesia, Digitalis—Chemistry, Digitalis—Biochemistry, General Pharmacology of Heavy Metals, Camphor and the Modern Analeptics. These topics are discussed in an interesting and thought-provoking, rather than an exhaustive, manner. An index is provided.

Hemorrhoids The Injection Treatment and Pruritus Ani By LAWRENCE GOTTBACH, M.D., Philadelphia. Second edition 207 pages, 31 illustrations. F. A. Davis Company, Philadelphia, 1931. Price, \$3.50 net.

This second edition of a manual on the treatment of hemorrhoids and pruritus ani by the injection method gives several changes in technique as compared to the first edition. The author's instruments and method of using 5 per cent phenolized oil are clearly set forth. Etiology, pathology and symptomatology are adequately pre-

sented and the book is well-printed and well-indexed

Rheumatic Fever—A Heart Disease By JOHN L. CHESTER, M.D., F.A.C.P., Attending Physician and Lecturer to the Training School, Providence Hospital, Detroit, Attending Physician and Chief of the Heart Service, Eloise Hospital, Eloise, Michigan 122 + 4 pages Privately printed, 1929

This is a concisely written monograph bringing together the best of recent advances in the field of rheumatic cardiac disease. It is illustrated by case reports from the cardiac service of Dr F. N. Wilson at the University of Michigan Hospital, Ann Arbor.

Lehrbuch der allgemeinen Physiologie Edited by ERNST GELLHORN, Ph.D., M.D., formerly Professor of Physiology at the University of Halle, Associate Professor of Physiology at the University of Oregon, Eugene, Oregon xiii + 741 pages, 126 illustrations. George Thieme, Leipzig, 1931. Price, in paper, M 47, bound, M 49.50.

In the preparation of this textbook of general physiology the editor named has had the aid of Professors Asher of Berne, von Buddenbrock of Kiel, Oppenheimer of Berlin, and Spek of Heidelberg. It treats physiology more particularly from the standpoint of recent advances in physico-chemistry. It should prove valuable to the more advanced students in the related fields of general biology, embryology and pathology, as well as to the physiologist.

Die Bakteriologie der Wurmfortsatzentzündung und der appendikulären Peritonitis By W. LOHR, Magdeburg, and L. RASSELD, viii + 96 pages, 46 illustrations and 11 tables. George Thieme, Leipzig, 1931. Price in stiff paper cover, M 12.

This well-arranged monograph deals with the bacterial content of the healthy and of the diseased appendix. It is based very largely upon original work consisting of cultural studies of appendices in sufficiently large series to make the results of significance. It is an important contribution to the subject of peritonitis of appendiceal origin.

College News Notes

Dr William Gerry Morgan (Fellow), Washington, D C, during the latter part of August was unanimously elected Dean of the Georgetown University School of Medicine by the University directors Dr Morgan will continue to serve as a Regent of the University, to which position he was appointed last June For many years, Dr Morgan has served on the medical faculty of Georgetown University Dr Morgan succeeds the late Dr John A Foote, who died several months ago Dr Morgan is the member of the Board of Governors of the American College of Physicians representing the general profession of the District of Columbia

At a recent meeting of the Board of Managers of the Goshen Hospital, Goshen, N. Y, Dr Louis F Bishop (Fellow) was appointed consulting cardiologist of the staff of consultants of the Goshen Hospital

Dr E J G Beardsley (Fellow), Philadelphia, addressed the Lehigh County Medical Society at Allentown, Pa, September 8, on "The Importance of Routine in Medical Diagnosis"

Dr. Roy C Mitchell (Fellow), Mount Airy, N C, presented a paper on the "Early Diagnosis of Carcinoma of the Stomach" at the meeting of the Eighth District Medical Society of North Carolina, October 2

The Inter-state Postgraduate Medical Association of North America held its annual meeting at Milwaukee, October 19-23, under the presidency of Dr. Henry A. Green (Fellow), Boston, Mass

Dr. Ed. H. J. (Fellow), Md
Secretary of the above Society

Under the Presidency of Surgeon General Hugh S Cumming (Fellow), U. S Public Health Service, Washington, D C, the American Public Health Association held its annual meeting in Montreal, Que, September 14-17

Dr J Feigenbaum (Associate) addressed the Montreal Clinical Society on September 9, 1931, upon the subject of "Constitution and Disease, Relating Particularly to Types Encountered in Peptic Ulcer, Gall Bladder Disease, Hypertension, and Exophthalmic Goiter"

Dr Frederick T Lord (Fellow), Boston, Mass, was elected president of the American Association for Thoracic Surgery at the fourteenth annual meeting held recently in San Francisco

Dr E J G Beardsley (Fellow), Philadelphia, addressed the Washington State Medical Association at Aberdeen, Washington, August 3, on "Cardiovascular Disorders of Every-day Practice" Dr Beardsley also held a clinic at the St Joseph Hospital, Aberdeen, on the morning of August 4

Dr. Howard L. Hull (Fellow), Elma, Washington, who has charge of the Oakhurst Sanitarium for Tuberculosis, acted as host to Dr Beardsley during his stay in the Evergreen State

Dr R. L. Hamilton (Fellow), Sayre, Pa, was among those who addressed the American Heart Association at its meeting in Philadelphia on June 6 Dr Hamilton's subject was "Precordial Pain Its Causes and Significance"

Dr Hyman I Goldstein (Associate), Camden, N J, is the author of the article

"Sterile Live Maggots in the Treatment of Osteomyelitis and Tuberculosis Abscesses," which appeared in the July, 1931, issue of Medical Review of Reviews Dr Goldstein also has an article appearing in the September, 1931, issue—"Hereditarily Familial Angiomatosis"

Dr James L. McCartney (Fellow), formerly Director, Bureau of Mental Hygiene, Connecticut State Department of Health, has been appointed psychiatrist with the New York State Department of Correction, and is stationed at the New York State Reformatory, Elmira, New York

Dr LeRoy S. Peters (Fellow), Albuquerque, N. M., presented a paper before the Los Angeles County Medical Society and the Hollywood Academy of Medicine on August 20

Dr Wann Langston (Fellow), Oklahoma City, Okla., has resigned as Superintendent of the University Hospital to become Professor of Clinical Medicine in the University of Oklahoma School of Medicine on a part-time basis. Dr Langston has opened his office at 502 Medical Arts Building for part-time practice in internal medicine

Dr Daniel E. S. Coleman (Fellow), New York, N. Y., is the author of an article, "Materia Medica—A Plea for Better Therapeutic Teaching," appearing in the August, 1931, issue of the Hahnemannian Monthly

Dr H. Beckett Lang (Fellow) has been appointed Clinical Director of the Marcy State Hospital at Marcy, New York

Dr Albert Warren Ferris (Fellow), after serving as Senior Assistant on the Staff of the Glen Springs, Watkins Glen, New York, for fifteen years in two terms of service, has retired from practice and resides at 111 N. Walnut Street, East Orange, N. J. Dr Ferris was previously President of the New York State Com-

mission in Lunacy, and Medical Editor of the International Encyclopedia

A medical clinic on Sero-fibrinous Pleurisy held by Dr. Carl V. Vischer (Fellow), Philadelphia, Associate Professor of Medicine at the Hahnemann Medical College, was published in the current issue of the Hahnemannian Monthly

Major Edgar Erskine Hume (Fellow), Medical Corps, U. S. Army, stationed at the Adjutant General's Office, State House, Boston, Mass., was under President Hoover's appointment, Secretary of the American Delegation to the International Congress of Military Medicine and Pharmacy at The Hague, Netherlands. There were ten United States delegates representing the U. S. Army, U. S. Navy, U. S. Public Health Service and the National Guard

Dr Fred M. F. Mervner (Fellow), Peoria, Ill., is the author of an article on "A Practical Classification of Heart Diseases," which appeared in the June, 1931, issue of the Peoria Medical News

Dr Harold G. F. Edwards (Fellow), Shreveport, La., is the author of an article on "A New Method for Studying Chest Films," appearing in the September, 1931, issue of Radiology

At a regular meeting of the Fulton County Medical Society on September 3, a bust of the late Dr. Elmore Callaway Thrash (Fellow), of Atlanta, Ga., was unveiled in the library of the Academy of Medicine at Atlanta.

Dr Horton Casparis (Fellow), Nashville, delivered a paper on "Allergy in Children" before the semi-annual meeting of the Southwestern Virginia Medical Society on September 24-25

Dr Francis H. Smith (Fellow), Abingdon, Va., also delivered a paper before the above meeting on "Coronary Disease as a Factor in Failing Myocardium"

Dr Samuel F. Thompson (Fellow), Kerrville, Texas, was re-elected President

of the Southwest Texas District Medical Society at its semi-annual meeting on July 13-14

Dr Waller S Leathers (Fellow), Dean, Vanderbilt University School of Medicine, Nashville, has been re-elected President of the National Board of Medical Examiners

Dr Luther C Davis (Fellow), Fairmont, W Va, has been appointed a member of the State Board of Nurses' Examiners to succeed the late Dr Harry M Hall (Fellow)

Dr William E Gardner (Fellow), Louisville, is Councilor for the Fifth District Medical Society, which was organized recently and is composed of physicians of Jefferson, Carroll, Trimble, Gallatin, Owen and Henry Counties (Kentucky) The new Society will meet twice a year

The following Fellows of the College were on the faculty of the Annual Summer Graduate Course at the Louisville City Hospital, held under the auspices of the Kentucky State Medical Association and the University of Louisville School of Medicine

Dr. Vugil E Simpson, Dr Philip F Barbour, and Dr Emmet F Horinc, all of Louisville

Dr Frank N Wilson (Fellow), Professor of Internal Medicine, University of Michigan Medical School Ann Arbor, presented four lectures on electrocardiographic studies, October 19-22 in a series held in the auditorium of Mount Sinai Hospital in connection with the graduate fortnight of the New York Academy of Medicine

The following Fellows of the College were on the faculty of the sixty-first annual session of the Colorado State Medical Association, September 13-17

Dr. J. H. Smith, D. C. — Clinical Medicine
Dr. J. H. Smith, D. C. — Clinical Medicine
Dr. J. H. Smith, D. C. — Clinical Medicine

Dr Henry S Plummer, Rochester, Minn — "Adenomatous and Exophthalmic Goiter"

Drs Lorenz W Frank (Fellow) and Clough T Burnett (Fellow), both of Denver, took part in a symposium on the arthritides, which was presented at the above meeting

The International Association of Industrial Accident Boards and Commissions held its eighteenth annual convention October 5-9 at Richmond, Va There were two medical sessions on Wednesday, October 7, the one in the morning was held under the Chairmanship of Dr G H Gehrmann (Fellow), Medical Director of the E I duPont de Nemours and Company, Inc, Wilmington, Del The following Fellows of the College were speakers at the morning session, as indicated.

Dr Henry Field Smyth, Philadelphia, — "Should a Course in Industrial Medicine be Included in the Curriculum of Medical Schools?" This paper was discussed by Dr J Allison Hodges (Fellow), President of the Medical Society of Virginia,

Drs J Morrison Hutcheson, Richmond, and Francis H Smith, Abingdon, discussed a paper entitled "Settlements as a Therapeutic Measure"

The following Fellows of the College were speakers at the afternoon session, as indicated

Dr R Finley Gayle, Richmond, discussed a paper on the "Care and Treatment of Injured to Avoid Traumatic Neurosis,"

Drs Warren T Vaughan and Dean Cole, both of Richmond, together discussed a paper on the "Differential Diagnosis of Traumatic and Occupational Chemical Injuries"

The fourth Graduate Fortnight of the New York Academy of Medicine was held October 19-30 in the general subject of "Disorders of the Circulation" and members of the College who participated in the program were:

Dr Warfield T Longcope (Fellow), Baltimore—"Syphilitic Aortitis,"

Dr Lewis A Comer (Fellow), New York City—"Pericarditis — Diagnosis and Medical Treatment,"

Dr Alfred Stengel (Master), Philadelphia—"Relation of Heart Disease to Operations,"

Dr Harlow Brooks (Fellow), New York City—"The Heart of an Athlete,"

Dr William Sydney Thayer (Fellow), Baltimore—"Endocarditis"

Dr Edward O Otis (Fellow), Exeter, N H, who has been Governor of the American College of Physicians for the State of New Hampshire for several years, was recently honored by a special meeting at the headquarters of the Boston Tuberculosis Association, commemorating the fiftieth anniversary of his service in the field of tuberculosis. Dr Frederick T Lord (Fellow), and Dr John B Hawes, 2d, (Fellow), were speakers. Dr Otis is a former President of the National Tuberculosis Association, Honorary President of the Massachusetts Tuberculosis League and Professor Emeritus of Pulmonary Diseases and Climatology at Tufts College Medical School. He is eighty-three years of age, and still engaged in active work.

The Medical Society of Virginia held its sixty-second annual session at Roanoke, October 6-8, under the Presidency of Dr J Allison Hodges (Fellow), Richmond. The following Fellows participated, as indicated:

Dr Warren T Vaughan, Richmond—"Arthritis Treated as a Form of Bacterial Allergy,"

Dr D C Wilson, University—"A Survey of Mental Disease in Virginia,"

Dr Beverley R Tucker, Richmond—"A Suggested Program of Mental Hygiene for Virginia,"

Dr Walter B Martin Norfolk—"Value of the Hormone Test for Early Pregnancy,"

Dr H B Mulholland University—"Diabetes in Children and Young Adults,"

Dr J Morrison Hutcheson, Richmond—"Physical Factors in Coronary Occlusion,"

Dr William B Porter, Richmond—"Angina Pectoris Associated with Pernicious Anemia"

Dr Edward C Mason (Fellow), Oklahoma City, Okla, is the author of an article entitled "The Modern Treatment of Burns," appearing in the August issue of the Journal of the Oklahoma State Medical Association.

Dr Lewis B Flinn (Fellow), Wilmington, Del, is the first President of the Academy of Medicine of Delaware, recently organized.

The Medical Society of the State of Pennsylvania held its eighty-first annual session at Scranton, Pa, October 5-8 under the Presidency of Dr Ross V Patterson (Fellow), Philadelphia. Dr Elmer H Funk (Fellow), Philadelphia, as Chairman of the Committee on Scientific Work, presented the program. Dr William H Mayer (Fellow), Pittsburgh, was installed as the new President for the coming year.

Fellows of the College who offered papers are listed below:

Dr Roy R Snowden, Pittsburgh—"Report of a Case of Osteomalacia,"

Dr George R Minot, Boston—"The Treatment of Anemia,"

Dr Sydney R Miller, Baltimore—"Contemporary Fads and Fallacies, Therapeutic and Diagnostic which Reflect Dangerous Professional Credulity"

Dr Henry K Mohler, Philadelphia—"Auricular Fibrillation—an Analysis of 220 Cases,"

Dr O H Perry Pepper Philadelphia—"Malignant Hypertension Simulating Brain Tumor"

Dr Willis F Manges Philadelphia—"Pulmonary Disease is the Result of Nasal Accessory Sinus Infection"

Dr Louis Humm Baltimore II—"Diagnosis of Obscure Fever"

Dr Charles C Wolferth, Philadelphia—"Indications for the Use of Laboratory Methods of Cardiovascular Diagnosis,"

Dr Edward L Bortz, Philadelphia—"Diffuse Gastric Hemorrhage with Special Reference to Dieulafoy's Ulcer,"

Dr Edgar M Green, Easton—"General Atelectasis of the Right Lung with the Heart Displaced to the Right of the Median Line and Left-Sided Pneumothorax,"

Dr John D Wilson, Scranton—"A Case of Xanthomatosis,"

Dr George Morris Piersol, Philadelphia—"Granulopenia,"

Dr Thomas Fitz-Hugh, Jr, Philadelphia—"Leukemoid Blood Reactions,"

Dr David Riesman, Philadelphia—"The Preoperative and Postoperative Treatment of Surgical Diseases of the Kidney from the Medical Standpoint,"

Dr E Bosworth McCready, Pittsburgh—"Relation of Endocrines to Juvenile Psychoses"

Dr Orlando H Petty (Fellow), Philadelphia, has been appointed Director of Public Health of the City of Philadelphia to fill out the term of Dr Andrew Carns, recently deceased

Dr Beaumont S Cornell (Fellow), Fort Wayne Ind, addressed the eighty-second annual session of the Indiana State Medical Association, which was held at Indianapolis September 23-25 on "Critical Review of Hypertension"

Dr Roscoe L Sensesch (Fellow) South Bend, Ind participated in a symposium on gastrointestinal diseases

Dr Walter S Leathers (Fellow), Nashville, was among the speakers at a conference of public health workers of Kentucky, Tennessee and Missouri, held at Louisville, Ind, September 21. Dr Leathers gave the paper "Medical Aspects of Tuberculosis in Public Health"

Drs Wardner D Ayer (Fellow), Syracuse, and Clayton W Greene (Fellow), Buffalo, are members of a Committee on Infantile Paralysis appointed by the President of the Medical Society of the State of New York to assist the Chairman of the Standing Committee on Public Health in devising means by which family physicians may aid in the control of the present epidemic

Dr Lewis J Morrman (Fellow), Oklahoma City, was appointed Dean of the University of Oklahoma School of Medicine

The thirty-seventh annual meeting of the Utah State Medical Association was held at Salt Lake City, September 9-11, under the Presidency of Dr William L Rich (Fellow). The following members of the College appeared on the program

Dr William C MacCarthy (Fellow), Rochester, Minn—"Why Cancer is so Frequently Hopeless,"

Dr Walter E Leonard (Associate), Los Angeles, Calif—"The Surgical Diabetic"

Dr Julius H Hess (Fellow), Chicago, addressed the American Dietetic Association, held at Cincinnati, October 19-21, on "Infant Feeding"

Drs Noble Wiley Jones (Fellow), Portland and Ralph C Maston (Fellow), Portland, addressed the Idaho State Medical Association's meeting on "Chronic Sinus Infection in Relation to Systemic Disease" and "Treatment of Impyema," respectively

Dr Frederick Tice (Fellow), Chicago, was recently appointed President of the Board of Directors of the Municipal Tuberculosis Sanatorium

Dr Walter M Simpson (Fellow), Dayton, and Dr Paul A O'Brien (Fellow), Rochester, Minn, addressed the 101st Annual Meeting of the American Medical Association at Atlantic City, N. J., September 21-25

ceral Syphilis', respectively, before the one hundred and eleventh meeting of the Michigan State Medical Society, held at Pontiac, September 22-24

The following Fellows of the College were among the guest speakers at the all-day session of the Northwestern Ohio Medical Association, Marion, Ohio, October 6

Dr Nathan S Davis III, Chicago—"Cardiac Infarction without Pain,"

Dr Julius H Hess, Chicago—"A Study of Premature Infants"

Acknowledgment is made of the following gifts of reprints by members to the College Library

Dr Miles J Breuer (Fellow), Lincoln, Neb—I reprint,

Dr A B Brower (Fellow), Dayton, Ohio—I reprint (with Dr Walter M Simpson (Fellow), Dayton, Ohio),

Dr Robert Chobot (Fellow), New York, N Y—I reprint,

Dr A Morris Ginsberg (Fellow), Kansas City, Mo—I reprint,

Dr. George B Lake (Associate), Highland Park, Ill—I4 reprints

OBITUARIES

DR LEONARD M MURRAY

Dr Leonard M Murray died suddenly at his home in Toronto, Saturday, August 8, 1931, under tragic circumstances. His family was abroad and unable to reach Toronto in time for the funeral which was held Thursday, August 13

Dr Murray was born in Truro, Nova Scotia, 1875. He graduated from McGill University Faculty of Medicine in 1900. He was sometime Provincial Pathologist of Nova Scotia and Professor of Pathology, Halifax Medical College, later Attending Physician, Halifax Children's Hospital and Professor of Medicine, Dalhousie University (Halifax). He served overseas during the War, at first in France and later at Bushy Park, England the Canadian Hospital for cardiovascular cases. In 1919 he came to Toronto as Consultant in Diseases of the Cardiovascular System, for what is now known as the Federal Department of Pensions and National Health. He was appointed to the Department of Medicine, University of Toronto, and to the Staff of the Toronto General Hospital for

the years 1919 to 1928, when he resigned largely on account of the pressure of work due to private practice and the departmental work at Christie Street Hospital

During his professional life he did postgraduate work in England, the United States, and abroad. He was a Fellow of the American College of Physicians and served on the Board of Regents for many years. He was elected a Fellow of the recently formed Royal College of Physicians and Surgeons of Canada in 1931. At the time of his death he was, in addition, a member of the Toronto Academy of Medicine, the Ontario and Canadian Medical Societies, the American Therapeutic Association and the Association for the Study of Internal Secretions. His later publications dealt entirely with diseases of the cardiovascular system.

The above is but a brief outline of his professional career. His advent to Toronto was a happy one for those of his friends who lived here. Strong bands of esteem and affection quickly were formed not only amongst the members of the medical profession but

as well amongst those who sought his advice and all who came in contact with him. There are those, not necessarily classed as cynics, who regard this as a real accomplishment. He was a member of The York Club and The Lambton Golf Club.

Saturday, August 8, was warm. Dr Murray had planned a fairly full day, which was begun by meeting two distinguished guests at the station early in the morning. This was followed by a foursome at golf during which he played a good game. That he nevertheless felt under some distress is evidenced by the fact that he took an early morning mixture of soda bicarbonate, repeating this after his return to his house in the early afternoon. He apparently refused to do more than rest for a short time before again driving to the hospital to see a patient. After his return from the hospital, he was in evident distress and to those of us who have learned his philosophical outlook on life, it is evident that he more than suspected his real condition. This time he took a stimulant but shortly after insisted upon receiving his guests who had been elsewhere for tea. As all were tired and the day hot, a short rest was welcomed before dressing for a dinner which was to take place later at The York Club. The chance call of one of the guests as to the time of dinner led to the discovery of his collapse and death but a few moments after he had seen that his house guests were comfortable. In the crucial few hours before he died, and while under distress, physical rather than medical judgment would be useless to the better

sorrow of many. The diagnosis would seem to be coronary thrombosis.

It is of professional interest to record that four electro-cardiographs had been taken, the last being in February, 1931. In his own phraseology, these fell within the accepted normal, except for a slight left ventricular preponderance. A more definite indication is given in that but a few days previously, in talking over the effect of golf on hot days with one of his colleagues, a slight amount of discomfort was mentioned.

In the delicious intimacy of an evening's relaxation amongst a few friends, which he so thoroughly enjoyed, Dr Murray had more than once declared that when he "went" he hoped he would go quickly, that he would be buried without "fuss or fumble" and "be forgotten." The first part of this wish has been fulfilled, the last, for his colleagues, for those who sought his advice or held his friendship, is impossible. His personality, charm, humor, sympathy and ability will in their memory endure for all time.

(Furnished by A. H. W. Canfield, M.D., F.A.C.P., Toronto.)

DOCTOR ELMORE CALLAWAY THRASH

Dr. Elmore Callaway Thrash (Fellow) died at Boulder Crest, Atlanta, Ga., on June 22, 1931, in his sixty-fifth year. Although the end came suddenly, it was not unexpected, as six months before he had developed a partial occlusion of a coronary artery. As an evidence of his devotion to duty and of his loyalty to his friends, shortly before his death he

attended the recent meeting of the American Medical Association as a member of the House of Delegates in order to serve as the representative of the medical profession of Georgia. On his return he was confined to his home up to the time of his death.

Dr Thrash was born in Meriwether County, Georgia on February 20, 1867. He was graduated with honors from the University of Louisville School of Medicine in 1891. He served as president of the Fulton County Medical Society and also the Medical Association of Georgia. In his early life Dr Thrash read a paper before the Medical Association of Georgia urging the establishment of a State Board of Health. This attracted so much attention that it was published in pamphlet form and distributed among the voters of the State. Soon after this the very efficient Georgia State Board of Health was organized.

In 1905 Dr Thrash was elected Professor of Pathology and Bacteriology in the Atlanta School of Medicine and he served in this capacity until 1914, in which year he was elected Professor of Diseases of the Chest in the Atlanta Medical College.

Dr Thrash always took a leading part in the various activities of the local, state and national medical associations. At these meetings he always stood for what was right, even if he stood alone. He read numerous papers dealing with pathology, bacteriology and internal medicine before medical societies throughout the nation and his views always commanded attention. Being a fluent speaker, having an alert mind, and a dis-

tinguished personality—which was unforgettable—he was probably better known than any other physician in the South.

On September 3, 1931, the medical profession of Atlanta presented to the Library of the Fulton County Medical Society a marble portrait bust of Dr Thrash as a tribute to his services to the medical profession and to mankind.

(Furnished by Jas N Brawner, M D, Atlanta, Ga.)

DOCTOR (LT COL) WILLIAM STEPHENS SHIELDS

Lt Col William Stephens Shields (Fellow), Medical Corps, U S Army, died, August 6, 1931, at the Letterman General Hospital, San Francisco, after an illness of about a year, aged 49 years.

Lt Col Shields was born at Washington, Georgia, and after completing his preliminary education, attended the Medico-Chirurgical College at Philadelphia, from which he received the degree of M D in 1906. He pursued postgraduate study at the Army Medical School and Columbia University, and was later a Fellow in Medicine under the Mayo Foundation. He was the author of a number of publications appearing in the Military Surgeon. He was a Fellow of the American Medical Association and was elected a Fellow of the American College of Physicians on November 17, 1928.

DR HENRY LALE WINTLER

Dr Henry Lale Winter (Fellow) Newburgh N Y died of heart disease July 29 1931, aged 63 years.

Dr Winter was born in Brooklyn, July 7, 1868, attended Brooklyn High School and later received his medical degree from New York University in 1892. He pursued postgraduate study in Munich, Nancy and Paris. He formerly held appointments as instructor in neurology at the University and Bellevue Hospital Medical College, associate in anthropology at the Pathological Institute of the New York State Hospitals for the Insane, and attending neurologist at the University and Bellevue Clinic. Dr Winter served during the World War, he was formerly president of the Board of Education of Cornwall. At the time of his death, he was consulting neurologist to Cornwall and St Luke's Hospitals.

Dr Winter was ex-vice president and ex-president of the Orange County Medical Society, a member of the Medical Society of the State of New York, a Fellow of the American Medical Association, and a member of the American Association for the Advancement of Science. He had been a Fellow of the American College of Physicians since April 10, 1917. He was the author of many articles, published in leading medical journals.

DR EDWARD P. SCHATZMAN

Dr Edward P. Schatzman (Associate), Pittsburgh, Pa., died July 27, 1931, of heart disease, aged 55 years. Dr Schatzman was a graduate of Western Pennsylvania Medical College, Pittsburgh in 1909. He was a member of the Nu Sigma Nu Fraternity, Allegheny County Medical So-

ciety, Pennsylvania State Medical Association, and the American Medical Association. He had been an Associate of the American College of Physicians since April 3, 1923. His practice had long been limited to internal medicine and diagnosis.

DR JOSEPH WITHAM YOUNG

Dr. Joseph Witham Young (Associate), Toledo, Ohio, died July 14, 1931, aged 54 years.

Dr Young received his B.S. degree from Cornell University in 1899 and his M.D. degree from Columbia University College of Physicians and Surgeons, 1903. From 1905 to 1906, he did postgraduate study in pathology and in internal medicine at the University of Berlin, and during 1919 in internal medicine at Harvard University Medical School. From 1906 to 1911, Dr Young resided in New York City, where he was assistant to the Out-patient Department of Bellevue Hospital and assistant in the Medical Department of the Vanderbilt Clinic. He had been a member of the staff of the Robinwood Hospital of Toledo since 1918.

Dr Young was a member of the Phi Delta Theta medical fraternity, a member and ex-chairman of the medical section of the Academy of Medicine of Toledo, a member of the Ohio State Medical Association, Northern Tri-State Medical Association, Northwestern Ohio Medical Association, and a Fellow of the American Medical Association. He had been an Associate of the American College of Physicians since April 3, 1922.

The Vital Hormone of the Adrenal Cortex*†

By FRANK A. HARTMAN, A.M., Ph.D., BYRON D. BOWEN, M.D., F.A.C.P.,
GEO. W. THORN, M.D., and CLAYTON W. GREENE, M.D., F.A.C.P.

IT HAS been known for many years that the adrenal glands are essential to life, but Wheeler and Vincent were the first to prove, at least in mammals, that the medulla was not essential. They found that as long as an adequate amount of cortex survived, destruction of all of the medullary tissue led to no ill effects.

The next step in the study of the cortex was the preparation of an extract containing the hormone. The cortex contains a sufficient amount of epinephrin to make the removal of the latter necessary, especially if the extract is to be concentrated.

In October, 1927, Rogoff and Stewart described the results obtained with two preparations, one a simple 0.9 per cent NaCl extract and the other a glycerol extract of the cortex. These methods do not eliminate the epinephrin and therefore definitely limit the amount of material which can be injected, on account of the epinephrin content of the extracts produced. Their report did not give the average survival of treated animals as compared with controls, although of thirty dogs treat-

ed six lived longer than the longest of the control animals.

In the same month Hartman, MacArthur and Hartman described a method for preparing an epinephrin-free cortical extract. With such an extract it was possible to increase markedly the survival period of completely adrenalectomized cats, the average survival period of all of the treated animals being twenty-one days as compared with six days for the untreated animals.

In March, 1930, Swingle and Pfiffner described a method of preparing a concentrated extract sufficiently potent to maintain the lives of adrenalectomized cats indefinitely. Their extract contained much epinephrin and inert material and was prepared by a long and complicated process.

In June, 1930, Hartman and Brownell described a simpler process for the preparation of a concentrated cortical extract. Their extract containing less than 1/100,000 epinephrin could be administered intravenously as well as subcutaneously. One patient has been injected subcutaneously four times daily for more than seven months without untoward results.

Experiments on animals have served as a basis for clinical work; therefore an outline of these results should precede the clinical studies.

*From the Departments of Physiology and of Medicine, University of Buffalo, Buffalo, N. Y.

†Presented at the Baltimore meeting of the American College of Physicians, March 26, 1931.

ANIMAL EXPERIMENTS

With the concentrated extract it is possible not only to maintain the lives of adrenalectomized animals indefinitely, but to enable such animals to live an apparently healthy existence (figure 1). One completely adrenalectomized cat was kept alive for 268 days and died because the extract was discontinued. Others have been kept alive for more than 150 days. This substance in the cortex which is essential to life has been called cortin.

Adrenalectomized cats treated with adequate cortin, eat well, gain in weight, play and fight. One female "came in heat" and became pregnant. The amount of extract required varies with the individual animal and also depends upon the stresses to which he is subjected. Until recently, in experi-

mental work upon cats, the adrenals have been removed in two stages a few days apart, because if both adrenals were removed at one operation the animal failed to make a good recovery and died in a few days. Now it is possible to remove both adrenals at one operation with excellent recovery if cortin is administered frequently. Such animals will apparently live indefinitely but they require much more cortin at least for a few weeks than those of the two-stage operation. We have removed both adrenals at one operation in three cats. At first the extract was given four times a day following bilateral adrenalectomy, then three times a day. The animals ate well and made a better recovery than many animals subjected to major operations not involving the adrenals. The



FIG. 1. Completely adrenalectomized cats kept in good condition by cortin.

reduction of extract caused loss of appetite and bloody feces in two, and bloody urine in the third. Increasing the extract caused complete recovery in all cases.

So far it has been impossible to produce overdosage phenomena.

By the administration of cortin one can revive adrenalectomized cats allowed to pass into the last stages of insufficiency preceding death. If the injections are intraperitoneal the effects begin to appear in less than an hour. If given subcutaneously it takes somewhat longer. One animal was allowed to go until there was marked prostration, dyspnea and muscular twitching. Intraperitoneal injection of cortin caused the disappearance of twitching and dyspnea within an hour, ten minutes later she was sitting up, forty minutes later she was eating. Recovery was complete.

Cortin appears to be essential for growth. If both adrenals are removed from young rats, a few continue to grow normally, some grow more slowly and others fail to grow at all, finally dying after days or weeks. Young adrenalectomized rats which are injected with adequate cortin all grow at about the normal rate. The females become pregnant and raise litters, then if the cortin is discontinued, some lose weight and die.

The operative wounds of adrenalectomy and other traumata heal slowly if an insufficient amount of cortin is administered but they heal normally if an adequate amount is given.

Cortin raises the resistance of adrenalectomized rats to bacterial toxins (Hartman and Scott, Perla and Marmonston-Gottesman). Seventy per cent

of the adrenalectomized rats injected with cortin survived a single dose of typhoid vaccine which killed all unprotected adrenalectomized rats. Cortin also protected adrenalectomized rats against increasing dosages of dead *Staphylococcus aureus*. The dosage had reached ten billions per day on the ninth day. At that time sixty per cent of the unprotected rats had died while all the treated ones were still alive and in fairly good condition.

Adrenalectomized animals are very sensitive to cold. When treated with an adequate amount of cortin, they resist cold almost as well as do normals. Two series of completely adrenalectomized rats of 20 and 19 rats respectively were exposed to a temperature which began at 56°F and gradually fell to 47°F in ten hours. One series had been injected twice daily with cortin, while the other series had been injected with the same volume of isotonic NaCl solution. Six normal rats were used as controls. Six hours after exposure to cold the average temperature (rectal) of the cortin-treated adrenalectomized rats was almost the same as that of the normals (98.8°F) while the average temperature of the NaCl-treated adrenalectomized rats was 91.8°F, excluding one that died. At the end of ten hours three more NaCl-treated rats had died while the average temperature of the remaining rats had fallen to 80.9°F. The temperature of the cortin-treated rats had fallen to 95.7°F as compared with 98.5°F for the normals.

The poor resistance to cold seems to be due to the inability to produce heat. We have been able to show that rats produce from 10 to 25 per cent less

heat after adrenalectomy. If, however, cortin is administered, heat production is maintained at almost normal levels.

The reduced heat production and lowered resistance to bacterial toxins are probably not specific but are merely manifestations of the reduced activity on the part of the body cells generally.

CLINICAL STUDIES

Since asthenia is one of the important manifestations of adrenal insufficiency, we have sought for a method of measuring it in the human.

Ergometer Test for Fatigue. In asthenia there is increased susceptibility to fatigue, although the muscular dynamic power may not decrease materially. Therefore the measurement of asthenia should test the threshold for fatigue rather than the strength of a single contraction. An ergometer can be used successfully to measure the fatigue threshold, provided certain precautions are observed.

The middle finger lifts weights swung by a chain over a pulley. The adjoining fingers on each side are supported in metal tubes while the hand is supported on a pad and held in place by a strap over the wrist. The working finger is connected to the chain by a leather thong or stall. The finger lifts the weight at every other beat of a metronome which is beating seconds. This is continued until the finger definitely fails to lift the weight up to a given mark. This end point is important and can be determined best by an experienced operator. The load chosen should be one that causes fatigue in about three to five minutes. It is

one test to another may be too large. If too light, the time required for the test is too long, in case marked improvement is subsequently shown. By not making tests too often improvement that might be brought about by training is avoided. The measure of fatigue is the work done (weight \times vertical distance raised \times number of contractions).

There seems to be less variation in the base level for fatigue in asthenic individuals than in some normal individuals.

For many years numerous workers have endeavored to relieve the symptoms of Addison's disease by the use of adrenal preparations. The earlier efforts have been without notable success, except that the Murrhead treatment has been somewhat effective in cases that were apparently not too severe. Within the past two years three groups of investigators have studied the effects of extracts of the adrenal cortex on clinical cases. Rogoff and Stewart in 1929 treated several patients with an extract administered by mouth. Improvement in symptoms occurred after several weeks of treatment. None of the cases reported seemed to be severe. In January, 1931, Rowntree, Greene, Swingle and Piffner reported their results in a number of cases of Addison's disease in which the extract prepared by Swingle and Piffner was administered subcutaneously or intravenously. The majority of their cases were benefited definitely. So far as we have been able to discover, no case has been treated in which there was complete or nearly complete adrenal insufficiency. We

in two cases of practically complete bilateral atrophy of the adrenal cortex and in a third case in which there appeared to be adrenal insufficiency of lesser degree

Case 1 A man of 24, a handy-man doing outdoor work for a gas company, was an athlete, specializing in basketball and baseball. In the winter of 1929-30 he noted fatigue in the evening, and he experienced gastro-intestinal upsets. These consisted of anorexia, nausea, and vomiting, and occurred with increasing severity and frequency during the succeeding spring

and early summer. In his previous history the only incident had been a febrile attack in 1928, which he said his family physician had diagnosed as "scarlet fever without the rash." Just previous to admission he had been ill for six weeks, showing weakness, epigastric distress, nausea, vomiting, and a loss of thirty to forty pounds in weight since the preceding winter. Upon admission to the hospital July 7, 1930, he was in a state of "collapse", irrational and nearly comatose (figure 2). His systolic blood pressure was 50 mm and his diastolic was 20 mm



FIG 2 Case 1 three days after admission to hospital

During the first twenty-four hours he received injections of salt solution, glucose and adrenalin subcutaneously, but was not improved. His legs twitched and his extremities were cold. During the second day he received the extract of 3200 grams of adrenal cortex which was given fractionally by frequent subcutaneous injections. On the third day he ate for the first time, seemed more alert, read a little, and did not sleep so much. The daily dose was then reduced to the equivalent of 500 grams of cortex. Gradual improvement took place (figure 3) and

the extract was diminished but on the twelfth day he had another relapse when he became almost as ill as he was upon admission. This relapse was occasioned by a further reduction in the extract. A second very severe case (Case 2) was admitted to the hospital at this time and it became necessary to divide the very limited supply of extract between the two, Case 1 receiving the larger portion. A large increase in the amount of extract brought his condition back to its former level of improvement (figure 4). Three subsequent relapses occurred, on the 55th,



July 14, 1930

FIG. 3. Case 1, 5th day, after beginning treatment.

86th, and 110th days after the institution of treatment. Each was caused apparently by a reduction of the amount of extract. It appeared from clinical observation that the daily administration of the extract from 1000 to 1200 grams of cortex was necessary to prevent the recurrence of symptoms. Also it seemed that injections every six hours were more effective than dosages fifty per cent greater given every eight hours.

It is probable that the amount of cortical hormone needed to obtain improvement in complete adrenal insufficiency, such as Case 1 represents, is much greater than that required for less severe cases such as have been reported from other clinics. In consequence, any question of potency of cortical extracts should be postponed until trial can be made on similar or the same cases. Our dosage has been based upon grams of fresh cortex. Our present extract contains in each cubic centimeter the product obtained from fifty grams of fresh material, although the earlier extract used in the first weeks in Case 1 represented fifteen grams per c c. When the extract was discontinued it required about three days for the recurrence of nausea, vomiting and asthenia, likewise about three days were necessary for complete recovery to the former level of improvement after the readministration of the extract. This cycle corresponds to the observations on adrenalectomized animals that are treated with the extract.

The blood pressure ranged from 85 to 100 systolic except during the relapses when it fell varying degrees. The temperature was usually about 97.0° F.

The blood urea which was 120 mgm on admission, fell promptly under treatment, but always rose when insufficient extract was given, while the blood sugar fluctuated considerably, reaching the low point, about 75 mgm, during relapses (figure 5).

During the first six and one-half months of treatment his clinical condition remained unchanged except for the short periods of relapse. The pigmentation however, increased very decidedly. His appetite, weight, and ability to work on the ergometer without fatigue remained about constant. From this time on he made further improvement. On the 224th day he could do six times more work than at the initial test on the ergometer; he had gained ten pounds in weight; his appetite had increased and he volunteered the information, "I can now walk quite fast." Data on the findings and the progress in this case are shown in the accompanying chart. The gaps indicate periods when he returned to his home in a nearby town. During these times he gave himself the injections. His first return to the hospital was because of a relapse, the second was for further study. His basal metabolism varied from minus 7 per cent to minus 15 per cent. While under observation in the hospital, after being out for a few hours one evening he developed an upper respiratory infection which persisted for seven days, with slight fever the first day. On the eighth day he had a chill, vomited and his temperature rose to 105.0° F. It was quite obvious that he had had an extension of his respiratory infection. His leucocytes were 30,000 with 84 per cent polymorphonuclears. The extract was



FIG. 3. Case 1 forty-five days after beginning cortin

increased to the limit available but he died in twenty-four hours

Autopsy Findings (A detailed report of the autopsy findings is to appear in *Endocrinology*) Addison's disease with marked atrophy of both adrenals, weight 3.44 gms. Old calcified tuberculosis of the mesenteric lymph-glands, and fresh tuberculous hyperplasia of a few mesenteric, and especially periaortic, periportal and peripancreatic lymphnodes, and a few anterior mediastinal nodes. Fresh lobular pneumonia of the right lower lobe. Fresh hemorrhage in the pleurae of both lungs, especially the left, also in a less degree in the mucosa of the stomach. Pseudo-melanosis of the cecum and appendix. Slight atrophy of the pancreas. Very slight atrophy of the heart. Slight splenic tumor. Chief diagnosis Addison's disease.

Case 2 This was a married woman 41 years of age, housewife, admitted to the hospital July 16, 1930. In 1925, five years before her admission to the hospital, her neighbors stated that she did not look well, her skin showed dark and light areas. At that time she was feeling fairly well and able to do her housework.

One year later she was treated for acute cholecystitis.

In 1927 she began to feel quite weak, had a poor appetite, was very nervous and restless, and could not sleep well. Her skin became much darker with the areas of vitiligo more prominent. She was seen by her physician at this time. Her blood pressure was 72 mm Hg, systolic. Diagnosis of Addison's disease was made. She remained in bed for one year, after which time she was up for only short intervals. Her blood

pressure remained between 66 and 72 mm Hg, systolic, and she gradually became weaker.

One year ago she had pleurisy and was in bed five weeks, after that she would be up part of the time. Her appetite was capricious. During the six weeks before admission she was in bed continuously.

There was no pain in the abdomen, but nausea and vomiting were present.

Physical examination revealed an adult female who was fairly well nourished. The skin was diffusely pigmented and showed scattered areas of vitiligo. There was no adenopathy. The chest was clear. Heart beat was quick, regular, no murmurs. Abdomen was negative. Blood pressure 60 mm systolic and 48 diastolic. Several small areas of pigment on the base of the tongue. No pigment in vagina, anus or rectum.

Laboratory findings Blood glucose 116 mgm, blood urea N 52.4 mgm, blood chlorides 534 mgm, blood uric acid 4.45 mgm. Urine normal. Blood count mild secondary anemia.

While in the hospital her blood pressure varied between 66 systolic and 48 diastolic, and 44 systolic and 28 diastolic. She became weaker, was nauseated and had some vomiting, epigastric pain, numbness and coldness in arms and legs. Before death which occurred three days after admission and two days after beginning treatment, pain in her legs was severe.

Autopsy Findings Pigmentation and vitiligo of skin, extreme atrophy of both adrenals, slight generalized passive congestion, healed tuberculosis of both apices, no active process, brown atrophy of the heart, recurrent chole-

cystitis, chronic lymphadenitis of lymph nodes of hilum of liver and pancreatic group, marked lymphoid infiltration and hyperplasia of thyroid

We believe that this patient should have received many times the amount of cortical extract that was administered to her but there was no more available

Case 3 A woman of 56 years who had had increasing fatigue and weakness for the past six years was admitted to the hospital Nov 19, 1930, for observation. She had been considered a case of hypothyroidism since 1921 and treated with thyroid which she stated brought about some improvement. Her blood pressure had been low during this period of observation. She also stated that brownish spots had appeared on her body during this time, but that her skin had always been dark. Three years before admission her physician had made a diagnosis of mild Addison's disease. She had lost some weight. Her blood pressure was 90 systolic and 60 diastolic. Her basal metabolism was low on several determinations—about minus 28 per cent. There was no pigmentation of the mucous membranes. She was under observation in the hospital for nine days before cortical extract was started during which time her ability to work on the ergometer without fatigue was established. Cortical extract was given twice daily subcutaneously for eight days, not including three days when it was omitted. Her ability to do work on the ergometer without fatigue was gradually increased, reaching a maximum of 2000 gm. work on the ergometer during the course of the treatment. During the time the extract was discontinued her ability to do work on the ergometer without fatigue was gradually decreased, reaching a minimum of 500 gm. work on the ergometer during the course of the treatment.

mained unchanged. After discharge from the hospital she was without treatment for fifty days, during which time her ability to work on the ergometer was two to three times greater than it had been before the institution of treatment. Thyroid, 0.12 to 0.18 gm daily, was then given until her basal metabolism was brought to normal, when her ergometer reading was eight times the original. Cortical extract was added to the thyroid medication daily for nine days and then omitted. Four days after the cortical extract was discontinued she could do thirty-eight times more work on the ergometer than originally (figure 6). The patient stated that she felt stronger when taking the combined thyroid and cortical extract, and showed distinct clinical improvement, with moderate increase in her blood pressure. This improvement, however, did not parallel the remarkable increase in her ergometer readings.

In a potent cortical extract we possess a substance which may perhaps serve as a therapeutic test in Addison's disease and which possibly may be of value in testing and treating other forms of adrenal insufficiency. Numerous investigators have used adrenal preparations in the treatment of hyperthyroidism. Shapiro and Marm reported the beneficial effect of a glycerol extract of the adrenal cortex in a case of Graves' disease. This was administered by mouth.

A boy of 19 years with clinical hypothyroidism, who had never received iodine, rested for three weeks in the hospital before treatment was started. During this time his basal metabolism remained between plus 25 and plus 35

per cent on several determinations Cortical extract was then given daily for eighteen days During this period he became able to do twice as much work on the ergometer as he had been able to do during the initial rest period After the extract was discontinued, this ability to work increased to three times There was no essential change in his basal metabolic rate In the cases of Graves' disease reported by Marine and his co-workers a drop in the basal metabolism did not occur until treatment had been going on for a much

longer period Unfortunately treatment in our case could not be continued longer

Experiences in the relief of muscular fatigue led us to try cortin for the relief of two cases of muscular atrophy in men over fifty In each case weakness began in the shoulder girdle In each the muscular fibrillation disappeared during treatment In one, an early case, the grip returned to normal in the hand affected In the other, marked muscular cramps disappeared, to return when treatment was discon-

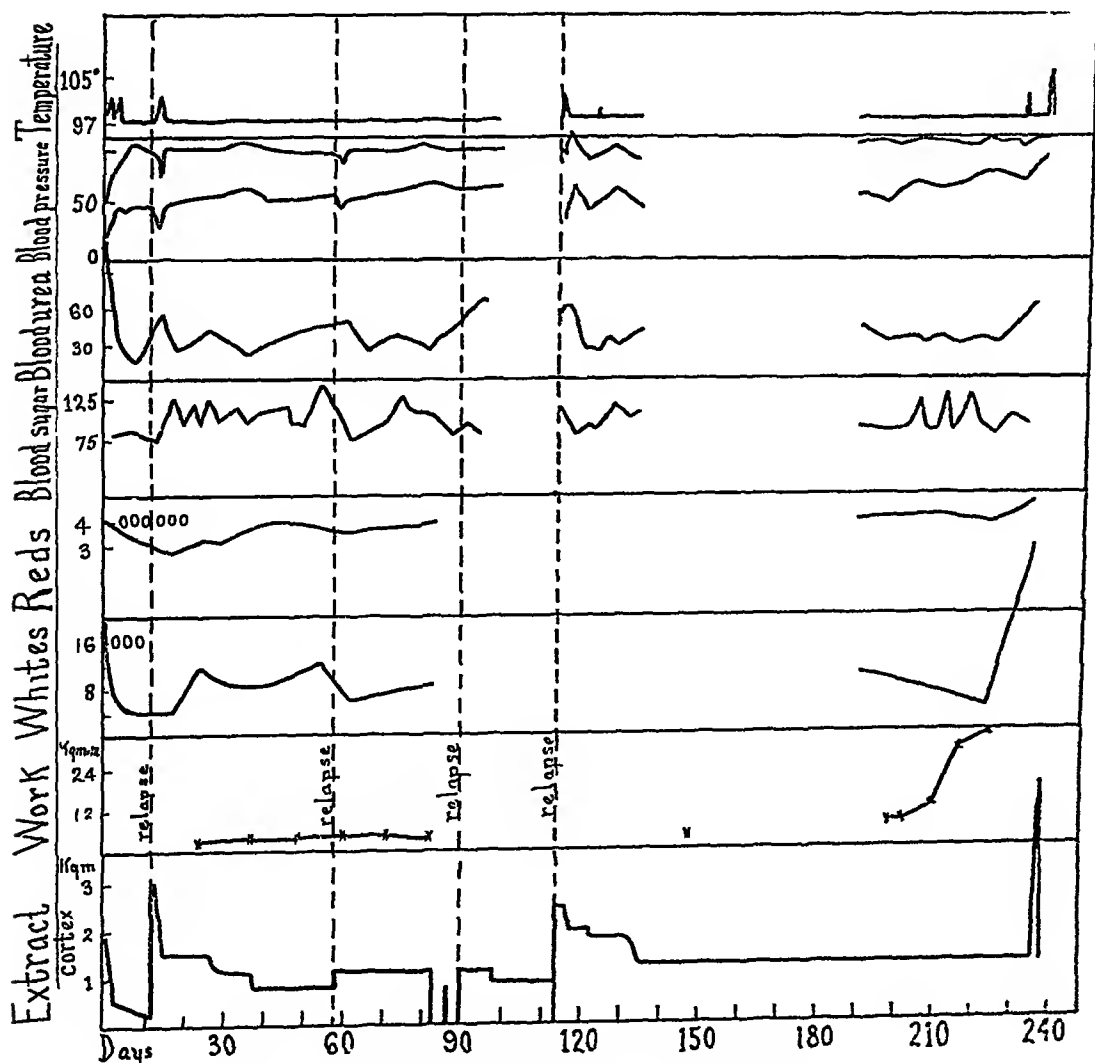


FIG 5 Chart showing various changes in Case 1

tinued. In a woman of 23 with the Landouzy-Déjérine type of muscular dystrophy treatment was followed by a marked increase in her capacity on the ergometer, and decidedly better rest during sleep

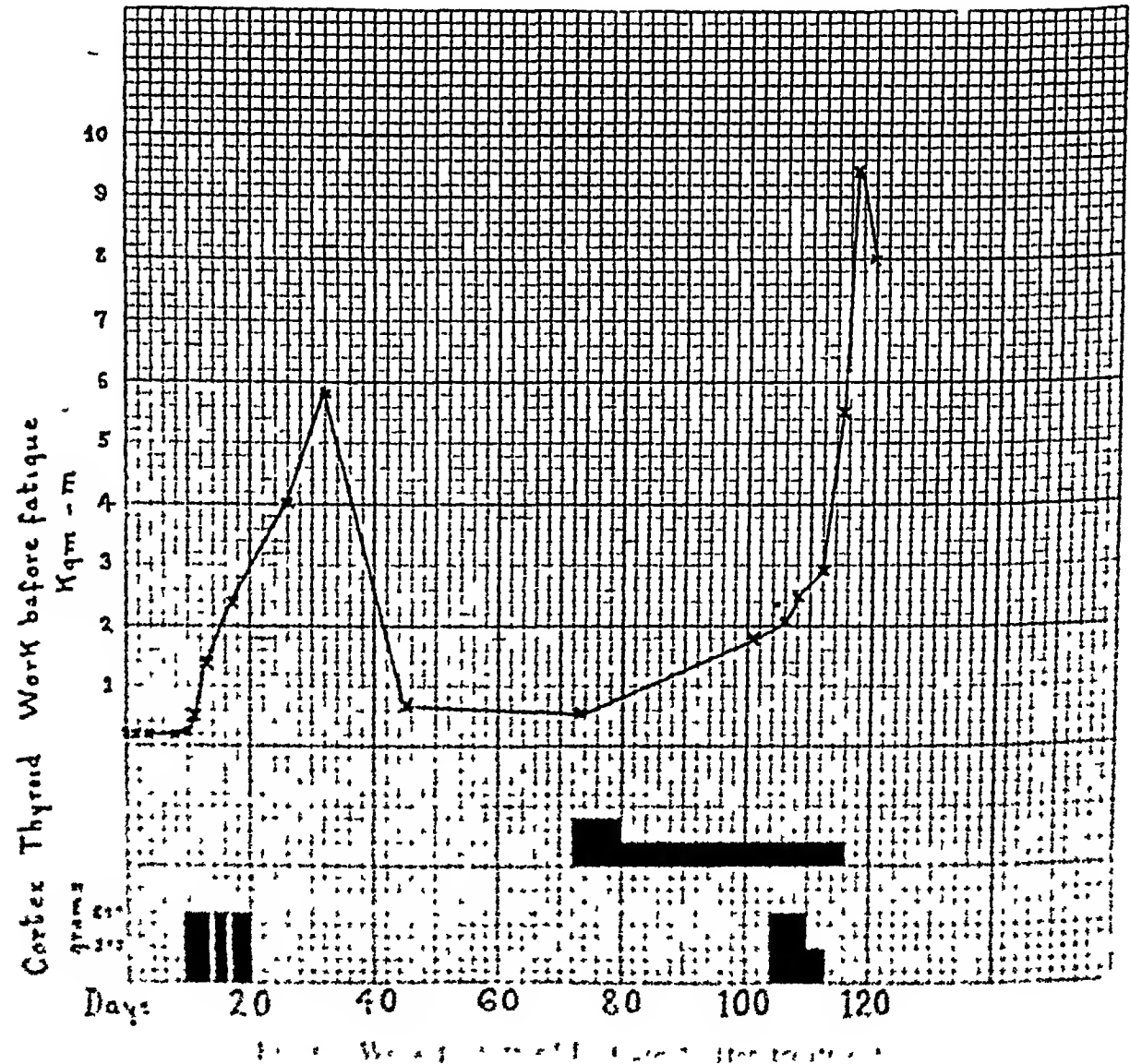
A few cases of marked post-infectious asthenia have shown clinical improvement following the use of cortin, with decided increase in capacity on the ergometer

SUMMARY

A potent cortical extract has been administered to two cases of practically complete adrenal insufficiency

In the first case it was of undoubted benefit Following its use the patient recovered from a very critical state That it kept him alive for nearly eight months was indicated by four definite relapses which followed its reduction or its discontinuance Readministration or increase of dosage in each relapse was followed by return to his former level He was making slow but definite improvement when bronchopneumonia caused his death

The period of treatment in the second case was obviously too short for observation to be of any value.



A third case, one of much less severity, has shown a remarkable increase in her ability to work without fatigue. Clinical improvement has not kept pace with this increase.

One case of hyperthyroidism has exhibited decided clinical improvement following the use of the extract alone.

Two cases of muscular atrophy and

one of muscular dystrophy have shown some improvement.

There is evidence that cortical extract reduces the asthenia which follows certain infections.

This study was aided by grants from the National Research Council and the Ella Sachs Plotz Foundation.

BIBLIOGRAPHY

- HARTMAN, FRANK A., AARON, A. H., and CULP, J. E. The use of cortin in Addison's disease, *Endocrinology*, 1930, xiv, 438.
- HARTMAN, FRANK A., and BROWNELL, KATHARINE A. The hormone of the adrenal cortex, *Proc Soc Exp Biol and Med*, 1930, xxvii, 938.
- HARTMAN, FRANK A., BROWNELL, KATHARINE A., and HARTMAN, WARREN E. A further study of the hormone of the adrenal cortex, *Am Jr Physiol*, 1930, xcv, 670.
- HARTMAN, F. A., MACARTHUR, C. G., and HARTMAN, W. E. A substance which prolongs the life of adrenalectomized cats, *Proc Soc Exp Biol and Med*, 1927, xxv, 69.
- HARTMAN, FRANK A., and SCOTT, W. J. MERLE. Protection of adrenalectomized animals against bacterial intoxication, *Proc Soc Exp Biol and Med*, 1931, xxviii, 478.
- PERLA, DAVID, and MARMORSTON-GOTTESMAN, J. Effect of injections of cortin on resistance of suprarenalectomized rats, *Proc Soc Exp Biol and Med*, 1931, xxviii, 475.
- ROGOFF, J. M., and STEWART, G. N. The influence of adrenal extracts on the survival period of adrenalectomized dogs, *Sci*, 1927, lxvi, 327.
- ROGOFF, J. M., and STEWART, G. N. Suprarenal cortical extracts in suprarenal insufficiency, *Jr Am Med Assoc*, 1929, xcii, 1569-1571.
- ROWNTREE, L. G., GREENE, C. H., SWINGLE, W. W., and PFEIFFER, J. J. Addison's disease, *Jr Am Med Assoc*, 1931, xcvi, 231.
- SHAPIRO, S., and MARINI, DAVID. Clinical report of a case of Graves' disease with rapid improvement following the oral administration of fresh ox suprarenal gland, *Endocrinology*, 1921, i, 699.
- SWINGLE, W. W., and PFEIFFER, J. J. An aqueous extract of the suprarenal cortex which maintains the life of bilaterally adrenalectomized cats, *Sci*, 1930, lxxi, 321.
- WHEELER, T. D., and VINCENT, S. The question of the relative importance to life of cortex and medulla of the adrenal bodies, *Trans Roy Soc Canada*, 1917, xi, 125.

The Relation of the Parathyroid Glands to Calcium Metabolism*†

By HAROLD A. BULGER, M.D., and DAVID P. BARR, M.D., F.A.C.P.,
St. Louis, Missouri

THE profound influence of the parathyroid glands on calcium metabolism is apparent from both experimental and clinical studies. Removal of these glands results in a marked decrease in serum calcium, tetany and in retention of calcium in the body. By means of the parathyroid extract of Collip^{1,2} it is possible not only to relieve the tetany but also to restore approximately normal conditions of calcium metabolism. Large doses of parathormone cause, in normal animals, hypercalcemia, hypotonicity of muscles, a great increase in the excretion of calcium in the urine, a deposit of calcium in the tissues and decalcification of bone. Furthermore Jaffe and Bodansky³ have recently shown that the injection of parathormone may form lesions resembling fibrous cysts in bone.

These changes from overdosage with parathyroid extract occur to a variable degree in different animals. Although several species are quite resistant the effect in man is well defined. The following following accidental complete

parathyroidectomy can be controlled over long periods. Hypercalcemia may be produced by large doses in individuals whose parathyroid glands are presumably normal. In Hunter's^{2,2} case of a house painter with lead poisoning, daily doses of 30 to 60 units of parathormone caused, in eleven days, a rise in serum calcium to 19.8 mg. A patient observed by Aub¹ demonstrates the source of the negative calcium balance in experimental hyperparathyroidism. This patient with otosclerosis was treated with parathormone for 42 days during which he lost 15 kilograms in weight, a change which would have accounted for 75 mg. of calcium if the loss of calcium had been derived from blood fluid and protoplasm. Actually he lost 170 grams of calcium which must have been derived from the bones.

Clinical hyperparathyroidism, presenting the identical features effected by injecting parathyroid extract is now recognized as a definite entity. It is encountered most often in association with the multiple lesions of osteitis fibrosa cystica (von Recklinghausen's disease of bone). In addition to bone cysts, giant cell tumor and general decalcification features which have been considered characteristic, there have been many cases of hyperplasia

*Presented at the meeting of the American Society of Experimental Pathology, St. Louis, Mo., Dec. 1934.

†Supported in part by a grant from the National Cancer Institute, U. S. Department of Health, Education and Welfare.

or tumor formation of the parathyroid glands, hypercalcemia, greatly increased calcium excretion in the urine, deposition of calcium in the tissues (the so-called metastatic calcification of Vichow) and occasionally the formation of stones in the urinary tract. The simulation of experimental hyperparathyroidism is so striking that there is reason to believe that the entire picture of osteitis fibrosa cystica is secondary to the increased activity of the parathyroid glands. Whether or not this be true, operation has demonstrated in a number of cases how completely the clinical condition can be arrested by removal of parathyroid tumors of hyperplastic parathyroid tissue. The effect upon the level of calcium in serum is well shown by Table I which includes the cases of osteitis fibrosa cystica in which parathyroid tissue has been removed for therapeutic effect.

In 16 out of 18 cases one or more tumors of the parathyroid gland were removed. The removal of the parathyroid tissue not only lowered the level of the calcium in the serum and transformed the previous negative balance into a retention of calcium but stopped the progress of the disease and arrested the formation of bone cysts and tumors. Recalcification of bone and recession of the cysts and tumors has been demonstrated. The marked drop in serum calcium indicated by the table was observed soon after operation and in many instances, although not all returned after a few weeks to a normal level. In the case of Barrenscheen and Gold⁴ a normal sized gland imbedded in the thymus was taken away without beneficial effect on the patient's symptoms and without change in the calcium level of the serum. In DuBois's¹⁴ case, however, two normal looking parathy-

TABLE I

	Calcium Milligrams Per Cent	
	Before Operation	After Operation
Barr, Bulger and Dixon ¹	16.6	4.1
Barr and Bulger ²	16.7	8.3
Barrenscheen and Gold ⁴	14.2	16.0
Beck ⁵	above normal	tetany
Boyd, Milgram and Stern ⁶	17.6	5.0
Compere ¹³	11.0	7.0
DuBois ¹⁴	16.5	13.9
Eggers ¹⁰	14.6	5.7
Gold ¹⁸	13.1	9.6
Hunter ²⁰	16.7	8.0
Hunter ²¹	15.0	6.7
Lanz ²⁷		
Mandl ²⁶	18.2	13.0
Olch and Bulger ²⁵	16.2	8.3
Pemberton and Geddie ¹¹	17.7	7.6
Quick and Hamburger ⁷	15.8	5.6
Snapper ¹⁷	23.6	6.6
Wilder ³⁸	13.2	7.1

roid glands were removed with apparent clinical improvement

Although osteitis fibrosa cystica may be the only condition which can be called with any probability a primary hyperparathyroidism, there are other bone diseases which may at times present comparable disturbances of calcium metabolism. Multiple myeloma is a condition accompanied by a high degree of bone destruction and it has been noted frequently in roentgenological examinations that there is a marked decalcification and rarefaction even in those portions of bone which are not actually involved in the tumor process. Metastatic calcification with deposit of calcium in lungs, gastric mucosa and kidneys has also been noted in multiple myeloma. Bulger and Barr¹⁰ studied a patient presenting these associations, including hypercalcemia, a negative calcium balance and metastatic calcification in whom there was generalized hyperplasia of the parathyroid glands. Apparently a similar condition may also occur in metastatic tumor of bone. Klemperer²⁴, in 1923, reported a case in which a tumor of the parathyroid gland was found in association with carcinoma of the breast and osseous metastases. It, therefore, appears that we may have a state in which hyperparathyroidism is associated with obviously primary bone disease. The following cases are presented as examples of this clinical picture.

Case 27-00 Barnes Hospital. This was a 55-year-old woman who had gradually increasing pains in the back for three years. She had gained weight and became very weak. She had been ill for several years and had been in the hospital several times. She had been treated with various drugs and had been in the hospital several times. She had been treated with various drugs and had been in the hospital several times. She had been treated with various drugs and had been in the hospital several times.

weakness became a prominent feature. Physical examination revealed marked pallor and great emaciation. There was evident mental depression and confusion. The red blood count was 1,900,000 with 35 to 40 per cent hemoglobin and a slight leucopenia. The non-protein nitrogen was 63 mgm per cent. The x-ray of the spine showed a general loss of calcium throughout, and narrowing of the bodies of the second lumbar, and ninth and twelfth dorsal vertebrae. The bony texture was uniform and the intravertebral spaces preserved. The pelvis showed irregularly outlined areas of rarefaction, the calvarium, clean-cut skull defects with some areas of marked mottling, indicative of an invasive process of finer type. The patient's serum calcium ranged from 15.8 to 16.5 mgm per cent. Probably because of the kidney insufficiency the serum phosphate was elevated to 6.3 mgm per cent. The non-protein nitrogen was 63 mgm per cent and the phenolsulphonphthalein excretion was only about 5 per cent. The urine showed a slight amount of albumin and a few granular casts. The urine also showed Bence-Jones' protein. The pathological process in the bones as revealed by x-ray was evidently malignant disease which was considered more like multiple myeloma than metastatic carcinoma. X-ray examination of the gastrointestinal tract and pyelograms of the urinary tract were negative. This patient died at home and no autopsy was made.

Case 27621 Barnes Hospital. This patient was a moderately obese woman, 49 years old, who had been bothered with chronic constipation. For about a year she had had dull pains in the lumbar and sacral regions and later in the left lower quadrant. She had recently shown evidence of mild diabetes mellitus. About three weeks before admission she collapsed from great weakness and began to have spells of nausea and vomiting. In the hospital her chief complaint was generalized weakness although at times the pain in her back was quite severe. She showed evidence of some loss of weight. The heart was moderately enlarged, regular and a little rapid. There was slight depression of the jugular venous pressure. The blood pressure was 170/120. The red blood count was 2,800,000 with 35 per cent hemoglobin.



FIG 1 Spine of Case 25209 showing general decalcification with narrowing of the bodies of the ninth and twelfth dorsal and second lumbar vertebrae

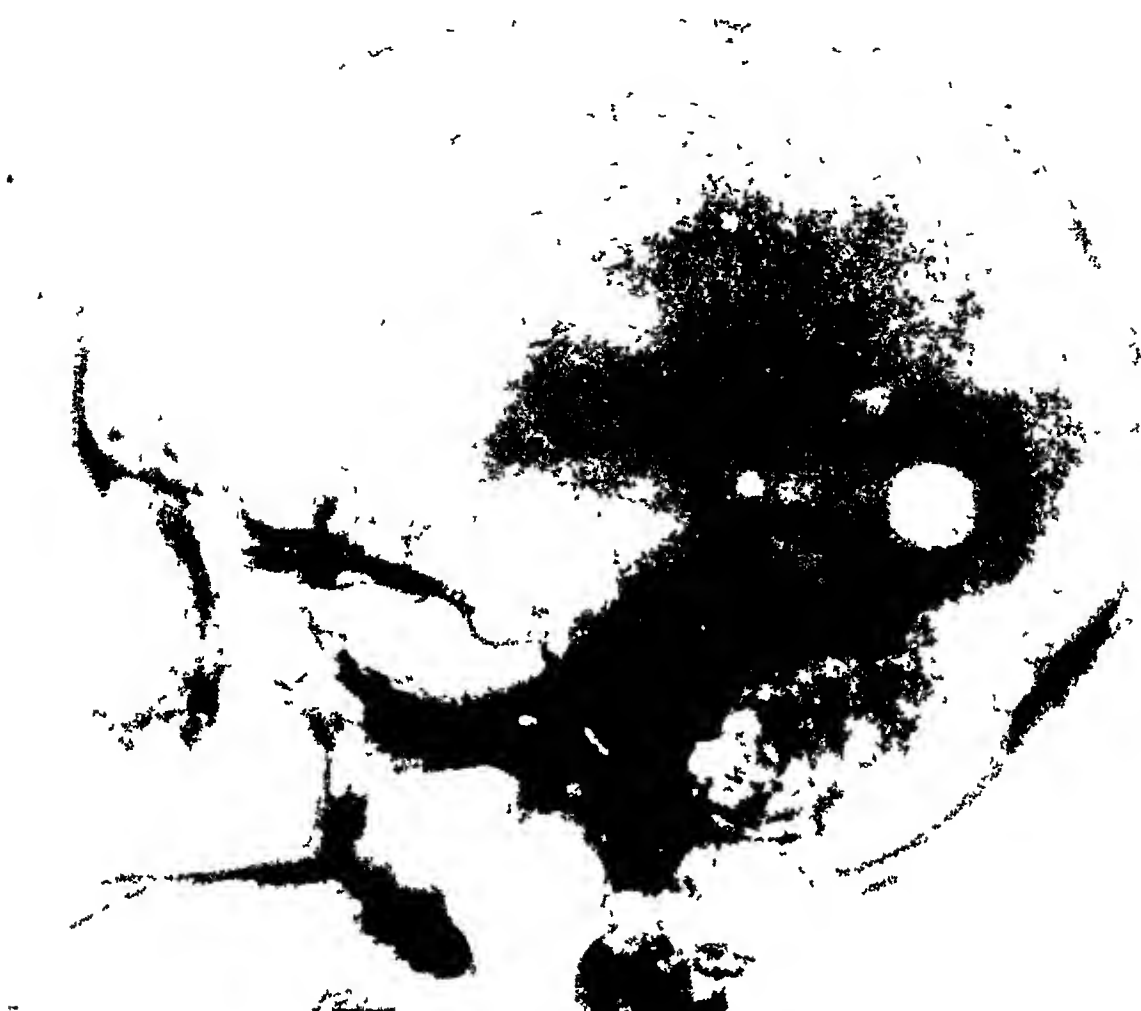


FIG. 2. Skull of Case 25209 showing clean cut bony defects with some areas of finer mottling

per cent hemoglobin. The non-protein nitrogen varied from 50 to 67 mgm. The urine contained a slight amount of albumin and numerous white blood cells. Bence-Jones protein was never demonstrated. X-ray examination of the spine showed a marked decrease in density throughout the bones and there was a symmetrical collapse of the fourth and sixth thoracic vertebrae. The third and sixth thoracic vertebrae also showed considerable loss of bony texture. It is noted that the radiographic changes in the greater than in the lesser thoracic vertebrae. The skull, however, showed no evidence of bony defects. The patient's clinical course was characterized by a gradual but steady decline in health, with increasing weakness and weight loss. The patient died on the 15th of the month.

tract did not reveal anything that could be considered a primary site. This patient's serum calcium ranged between 16.5 and 18.3 mgm per cent, phosphate between 4.0 and 4.9 mgm per cent. Further studies showed she was on a slightly negative calcium balance. The amount of calcium excreted in the urine was greater than would have been expected with the demonstrated degree of kidney insufficiency. Since discharge from the hospital he has been failing slowly.

Case 22810. Barns Hospital. This was a 50-year-old male who had been treated for a chronic depressive psychosis for many years. He had a long history of mental illness, with periods of remission and exacerbation. The patient's physical examination was unremarkable, and his laboratory studies showed no significant abnormalities. The patient's clinical course was characterized by a gradual but steady decline in health, with increasing weakness and weight loss. The patient died on the 15th of the month.



FIG 3 Spine of Case 27621 showing general decalcification with collapse of the body of the fourth dorsal vertebra and slighter changes in third and sixth dorsal vertebrae



FIG. 4 Calvarium of Case 27621 showing multiple areas of rarefaction

decalcification in the pelvis. Later consideration showed that the lesser trochanter of the right femur could not be seen (figure 5). In three months she was again complaining of the same pains in the right leg. X-rays then revealed that in this short interval an extraordinary degree of decalcification had occurred with rarefaction of the head and neck of the femur and with loss of bone substance in the neck of the right femur and the upper portion of the acetabulum (figure 6). Similar changes were noted in the iliac portion of the right pelvis and the lesser trochanter of the femur. There was a large fracture of the neck of the right femur with displacement of the fragments. X-rays also showed that the head and neck of the femur were completely destroyed and that the lesser trochanter was also destroyed.

marked hypercalcemia, the serum calcium ranging from 135 to 151 mgm per cent, low serum phosphate varying from 25 to 26 mgm per cent. Shortly after x-rays were taken she fractured her right femur, an injury which she survived for only five months. Autopsy revealed hypernephroma involving the adrenal, both kidneys, the femur and pelvis. The acetabulum was entirely destroyed and there was a large tumor mass extending into the pelvis from the right side and pressing on the rectum. It is most unfortunate that permission to examine the parathyroid glands was not obtained. Of particular interest in the post-mortem examination were the kidneys which showed a deposit of calcium about the tubules similar to metastatic calcium deposits.



FIG 5 X-ray of right hip of Case 22810 taken at time of admission to the hospital and showing abnormal area of calcification in pelvis, absence of lesser trochanter but little other evidence of decalcification or destruction



Figure 1. A large, dark, irregular shape on the right side of the image, possibly a shadow or a biological specimen, against a light background. The shape has a curved, almost circular upper portion and a more elongated, pointed lower portion. The texture of the dark area is grainy and noisy. Below this main shape, there is a smaller, dark, vertical, elongated object, possibly a shadow or a small specimen, also with a grainy texture.

quite like that previously described with osteitis fibrosa cystica and multiple myeloma

Cases with malignant disease of bone presenting hypercalcemia are listed in Table II

ties are like those found in hypoparathyroidism but the bone pathology and negative calcium balance are distinctly different. It would seem that the hyperplasia of the parathyroid glands

TABLE II

Condition	Author	Calcium Mgm Per Cent
Proven cases of multiple myeloma	Carlton ¹¹ Durman ¹⁵ Barr and Bulger ² Bulger ¹⁰ Soper and Stroud ³⁶	120 to 160 161 160 to 178 134 126 to 160
Myeloma or metastatic tumor of bone	Francis Smith ³⁴ Francis Smith ³⁴ Belden ⁸ No 25209 No 27621	160 (approx) 160 (approx) 153 to 187 158 to 165 165 to 183
Metastatic tumor of bone	No 22810	135 to 151

Parathyroid hyperplasia has been demonstrated by Erdheim¹⁷ in spontaneous rickets in animals, and by Pappenheimer and Minor³⁰ in rickets in children. Enlargement of the parathyroid has been recorded in osteomalacia. These findings raise the question as to the relation of the parathyroid glands to the disturbed calcium metabolism of these conditions. One finds in rickets and osteomalacia abnormalities of calcium metabolism quite distinct from those characteristic of hyperparathyroidism. In contrast to hyperparathyroidism one finds in both conditions a tendency toward a low serum calcium and tetany. Both have an increased elimination by the gastro-intestinal tract but very small amounts of calcium in the urine. Therefore, it does not appear that there is any direct relation between the abnormalities presented and an increased activity of the parathyroids. Some of the abnormali-

ties in rickets and osteomalacia is not a primary factor but is of the nature of a compensating mechanism. It might be noted that parathormone will relieve the tetany of both conditions and we have noted the transformation of a negative into a positive calcium balance in a case of osteomalacia on administration of parathormone.

The principal condition responsible for the development of rickets and osteomalacia is a deficiency of ultraviolet radiation and vitamin D. The relationship between these factors and the activities of the hormone of the parathyroid glands is so intimate that their functions in relation to calcium metabolism cannot well be discussed separately. The action of large amounts of vitamin D (irradiated ergosterol) is strikingly like parathyroid extract. It causes an increase in calcium in the serum, metastatic calcification and an increased excretion of calcium in the



quite like that previously described with osteitis fibrosa cystica and multiple myeloma

Cases with malignant disease of bone presenting hypercalcemia are listed in Table II

ties are like those found in hypoparathyroidism but the bone pathology and negative calcium balance are distinctly different. It would seem that the hyperplasia of the parathyroid glands

TABLE II

Condition	Author	Calcium Mgm Per Cent
Proven cases of multiple myeloma	Carlton ¹¹	120 to 160
	Durman ¹⁵	161
	Barr and Bulger ²	160 to 178
	Bulger ¹⁰	134
	Soper and Stroud ³⁶	126 to 160
Myeloma or metastatic tumor of bone	Francis Smith ³⁴	160 (approx)
	Francis Smith ³⁴	160 (approx)
	Belden ⁶	153 to 187
	No 25209	158 to 165
	No 27621	165 to 183
Metastatic tumor of bone	No 22810	135 to 151

Parathyroid hyperplasia has been demonstrated by Erdheim¹⁷ in spontaneous rickets in animals, and by Pappenheimer and Minor³⁰ in rickets in children. Enlargement of the parathyroid has been recorded in osteomalacia. These findings raise the question as to the relation of the parathyroid glands to the disturbed calcium metabolism of these conditions. One finds in rickets and osteomalacia abnormalities of calcium metabolism quite distinct from those characteristic of hyperparathyroidism. In contrast to hyperparathyroidism one finds in both conditions a tendency toward a low serum calcium and tetany. Both have an increased elimination by the gastro-intestinal tract but very small amounts of calcium in the urine. Therefore it does not appear that there is any direct relation between the abnormalities presented and an increased activity of the parathyroids. Some of the abnormali-

ties are like those found in hypoparathyroidism but the bone pathology and negative calcium balance are distinctly different. It might be noted that parathormone will relieve the tetany of both conditions and we have noted the transformation of a negative into a positive calcium balance in a case of osteomalacia on administration of parathormone.

The principal condition responsible for the development of rickets and osteomalacia is a deficiency of ultra-violet radiation and vitamin D. The relationship between these factors and the activities of the hormone of the parathyroid glands is so intimate that their functions in relation to calcium metabolism cannot well be discussed separately. The action of large amounts of vitamin D (irradiated ergosterol) is strikingly like parathyroid extract. It causes an increase in calcium in the serum, metastatic calcification and an increased excretion of calcium in the

urine Absence of vitamin D may cause a decrease in serum calcium and tetany Several authors have suggested that vitamin D exerts its influence by directly stimulating the parathyroid glands Morgan and Garrison²⁷ have demonstrated, however, that there is actually a variation in effectiveness of parathormone depending upon the amount of vitamin D in the body. The experiments of Rosello and Petrillo³³ have indicated that after the absence of radiant energy for some time parathyroid extract is relatively inactive Again, it has been shown that after removing the parathyroid glands, vitamin D is much less active It appears, indeed, that the more thoroughly parathyroid tissue is removed, the less effective is vitamin D Taylor, Branion and Kay³⁷ showed that when complete eradication of parathyroid tissue is assured by removing all tissue of the region including the thymus, huge doses of irradiated ergosterol were required to raise the calcium of the blood Thus some doubt is cast upon its efficacy It should be noted, however, that Pappenheimer²⁹ has demonstrated that cod liver oil and irradiated ergosterol in therapeutic doses are antirachitic in the absence of the parathyroid glands

The clinical diagnosis of hypoparathyroidism may be indicated by the history of thyroidectomy and the occurrence of tetany In the opposite condition of hyperparathyroidism, tumors in the region of the thyroid have occasionally been palpated but are easily confused with adenomata of the thyroid gland Ordinarily disturbances in calcium metabolism offer the best evidence of abnormal parathy-

roid function and consist of changes in the level of serum calcium, in the excessive excretion of calcium in the urine, in decalcification of the skeleton and deposit of calcium in the tissues Metastatic calcification can be discovered only at autopsy while the determination of calcium balance is much too cumbersome, difficult and time-consuming to be applied as a clinical test The level of serum calcium remains, therefore, as the most readily ascertainable diagnostic method It is of interest to consider to what extent disturbances in the level of serum calcium reflect changes in parathyroid function and to inquire what factors other than the parathyroids may influence calcium values

It is important to emphasize the remarkable constancy of the serum calcium and that such an adjustment to a definite level is quite necessary because fluctuation in the concentration of calcium may cause profound changes in many physiological processes The activity of the parathyroid glands appears to be concerned, primarily, with this regulatory mechanism It is surprising that administering large quantities of calcium by mouth may have little or no influence on the amount of calcium in the blood After administering calcium salts intravenously the calcium in the blood promptly returns to normal Rapid destruction of bone may cause no rise in serum calcium With extensive malignant disease of bone, after comminuted fractures and with bone atrophy from disuse, serum calcium may be quite normal

Other factors may influence the level of calcium in the blood Aside from the fluctuations of serum calcium re-

lated to vitamin D or parathyroid activity, the two factors which have a significant influence on calcium are the concentrations of serum phosphate and serum protein. The calcium will rise and fall directly with the protein although the changes due to this factor are not great. Conditions producing a high serum phosphate, however, may be attended by a considerable reduction in the calcium. This phenomenon is most commonly seen in chronic nephritis with phosphate retention. It should also be noted that low serum calcium and even tetany may be associated with chronic diarrhea.

While the estimation of serum calcium is of undoubted diagnostic importance in indicating hyperparathyroidism, it appears that there may be an increased activity of these glands with an increased excretion of calcium and a large amount of calcium in the urine without obvious rise in the serum calcium. Aub¹ notes that 50 units of parathormone may not markedly influence the serum calcium level of a normal individual, while approximately doubling the excretion. Three of the cases included in Table I had relatively normal serum calcium although they were undoubtedly examples of clinical hyperparathyroidism and responded typically following the removal of parathyroid tumors. The bone lesions similar to those of clinical hyperparathyroidism which Jaffe and Bodansky²³ have apparently produced in animals are not necessarily accompanied by any increase in the serum calcium. It appears that patients with hyperparathyroidism who develop marked kidney insufficiency may have enough phosphate retention in the

blood to maintain a normal serum calcium. Bulger, Dixon and Barr¹⁰ have described in detail their experiences in reducing calcium to normal in two patients with hyperparathyroidism by administering phosphate solutions by mouth. This undoubtedly did not change the activity of the parathyroids but produced the effect by increasing the phosphate in the blood.

Hypercalcemia was noted clinically by Hess and Lewis¹⁹ in children who were receiving relatively large amounts of the irradiated ergosterol but it seems unlikely that this would be encountered in the average clinical experience and under the circumstances would hardly be confused with hyperparathyroidism. The occurrence of high serum calcium reported in gout and chronic arthritis has not been confirmed. High serum calcium was noted by Brown and Roth⁹ in polycythemia, but Benedict and Turner⁷, in a study of nine cases, did not find these high values. In three cases of polycythemia observed in this clinic the calcium was normal. It seems doubtful that any factors of clinical importance other than an increased activity of the parathyroids will cause a definite and continuous elevation of the serum calcium.

CONCLUSIONS

The influence of the parathyroid glands on calcium metabolism is apparent not only after removal of the parathyroids and the administration of parathyroid extract but also in clinical hyperparathyroidism a condition which appears most often in association with osteitis fibrosa cystica but also with multiple myeloma and metastatic tumors of bone.

The level of serum calcium is the best index of parathyroid function and is of such diagnostic importance that its use as a test should be applied in all cases with general disease of bone and in all conditions in which there may be a disturbance of calcium metabolism. The serum calcium, however, does not always reflect either disturbances of calcium metabolism or changed activity of the parathyroid glands. It may be normal even with

marked disturbances of calcium metabolism. In evident hyperparathyroidism it appears that serum calcium may occasionally be within normal limits. Low serum calcium may be due to a lack of vitamin D or to an increase of phosphate in the serum. These conditions, however, are not likely to be confused with hypoparathyroidism. Hypercalcemia usually indicates an increased activity of the parathyroid glands.

REFERENCES

- ¹AUB, J C. Calcium and phosphorus metabolism, Series 24, 1928-29 Harvey Lectures.
- ²BARR, D P, and BULGER, H A. The clinical syndrome of hyperparathyroidism, *Am Jr Med Sci*, 1930, clxxix, 449.
- ³BARR, D P, BULGER, H A, and DIXON, H H. Hyperparathyroidism, *Jr Am Med Assoc*, 1929, xcii, 951.
- ⁴BARRENSCHEN, H K, and GOLD, E. Kalkuntersuchungen bei Skeletterkrankungen, *Wien med Wchnschr*, 1928, lxxviii, 1340.
- ⁵BECK, A. *Arch f klin Chir*, 1928, clii, 123.
- ⁶BILDEN, W. Bone disease, *Radiology*, 1928, xi, 280.
- ⁷BENEDICT ETHGL M, and TURNER, K B. The serum calcium in polycythemia vera, *Jr Clin Invest*, 1930, ix, 263.
- ⁸BOYD, J D, MILGRAM, J E, and STERN, G. Clinical hyperparathyroidism, *Jr Am Med Assoc*, 1929, xciii, 684.
- ⁹BROWN, G E, and ROTH, G M. The reduction of hypercalcemia in cases of polycythemia vera by phenylhydrazine, *Jr Clin Invest*, 1928, vi, 159.
- ¹⁰BULGER, H A, DIXON, H H, and BARR, D P. Functional pathology of hyperparathyroidism, *Jr Clin Invest*, 1930, ix, 143.
- ¹¹CHARLTON, T J. Multiple myeloma, *Arch Int Med*, 1927, xl, 105.
- ¹²COOPER, J B. The parathyroid glands, *Medicine*, 1926, v, 1.
- ¹³COMPÈRE, E L. Bone changes in hyperparathyroidism, *Surg, Gyn and Obst* 1930, l, 783.
- ¹⁴DUBOIS, E F, ALBRIGHT, F., HANNON, R R, SHORR, E, MCCLELLAN, W S, BAUER, W, and AUB, J C. A case of osteitis fibrosa cystica (osteomalacia?) with evidence of hyperactivity of the parathyroid bodies, *Jr Clin Invest*, 1930, viii, 215.
- ¹⁵DURMAN, D C. Myeloma of the spine, *Ann Surg*, 1928, lxxxviii, 975.
- ¹⁶EGGERS (Quoted by Mandl²⁰).
- ¹⁷ERDHEIM, J. Rachitis und Epithelkörperchen, *Wien*, 1914.
- ¹⁸GOLD, E. Über die Bedeutung der Epithelkörpervergrößerung bei der Osteitis fibrosa generalisata (Recklinghausen), *Mitt ad Grenzgb d Med u Chir*, 1928, xli, 63.
- ¹⁹HESS, A F, and LEWIS, J M. Clinical experience with irradiated ergosterol, *Jr Am Med Assoc*, 1928, xci, 783.
- ²⁰HUNTER, D. Hyperparathyroidism (hyperfunction of a parathyroid tumor in a case of generalized osteitis fibrosa), *Proc Royal Soc Med*, 1929, xxiii, 227.
- ²¹HUNTER, D. Hyperparathyroidism general osteitis fibrosa with multiple osteoclastomata, *Proc Royal Soc Med*, 1931, xxiv, 486.
- ²²HUNTER, D. Goulstonian lecture significance to clinical medicine of studies in calcium and phosphorus metabolism *Lancet*, 1930, i, 897-947 and 999.

- ²³JAFFE, H L, and BODANSKY, A Experimental fibrous osteodystrophy (osteitis fibrosa) in hyperparathyroid dogs, Jr Exp Med, 1930, lII, 669
- ²⁴KLEMPERER, P Parathyroid hyperplasia and bone destruction in general carcinomatosis, Surg Gyn and Obst, 1923, XXXVI, II
- ²⁵LANZ (Quoted by Mandl²⁰)
- ²⁶MANDL, F Zur Frage der Exstirpation eines Epithelkorpertumor bei der allgemeinen Osteitis fibrosa, Zentralbl f Chir, 1929, lvi, 1739
- ²⁷MORGAN, AGNES D, and GARRISON, E A The effect of vitamin D and reactions of diet, their response to parathyroid extract, Jr Biol Chem, 1930, lxxxv, 687
- ²⁸OLCH, I Y and BUICER, H A (To be published)
- ²⁹PAPPENHEIMER, A M The antirachitic action of cod liver oil and irradiated ergosterol in parathyroidectomized and thymectomized rats, Jr Exp Med, 1930, lII, 805
- ³⁰PAPPENHEIMER, A M, and MINOR, JOHN Hyperplasia of parathyroids in human rickets, Jr Med Research, 1921, xII, 391
- ³¹PEMBERTON, J, and GEDDIE, K B Hyperparathyroidism, Ann Surg, 1930, LCHI, 202
- ³²QUICK, A J, and HUNISBERGER, A Hyperparathyroidism, Jr Am Med Assoc, 1931, xcvi, 745
- ³³ROSELLO, H, and PETRILLO, L M A note on the relation of light to the action of parathyroid extract, Endocrinology, 1928, xII, 797
- ³⁴SMITH, F M (Personal communication to the authors)
- ³⁵SNAPPER, I Gezwel van een Byschildklier en Skeletafwijkingen Nederlandsch Tijdschrift voor geneeskunde, 1929, lXXIII, 4758
- ³⁶SOPER, H, and STROUD, C M (Personal communication to the authors)
- ³⁷TAYLOR, N B, BRANION, J D, and KAY, H D Some effects of the administration of excessive doses of irradiated ergosterol to normal and to parathyroidectomized dogs, Jr Phys, 1930, LXX, 35
- ³⁸WILDER, RUSSELL M Hyperparathyroidism tumor of the parathyroid glands associated with osteitis fibrosa, Endocrinology, 1929, xII, 231

The Etiology and Treatment of Diabetes Insipidus*†

By T B FUTCHER, M B , F A C P , *Baltimore, Md*

THE chief purpose of this paper is to recount briefly the historical development of our knowledge concerning the etiology of diabetes insipidus up to the present time

According to Hirsch, the earliest account of a sweet taste of the urine in certain patients comes from India and is to be found in the Ayur Veda of Sutra. Although certain symptoms of diabetes were known to the Greek, Roman and Arabian physicians, it remained for Celsus, a Roman physician, in the latter half of the second century of the Christian era to describe its outstanding symptoms. Aretaeus, of Cappadocia, a Greek physician practicing in Rome, and a contemporary of Celsus, is said to have first used the word diabetes (*διαβήτης*, a siphon). These early accounts deal with the saccharine type.

Thomas Willis, Sidley Professor in Oxford University, in his "Pharmaceutice Rationalis" published in 1674, was the first European to describe the sweet taste of the urine, and he is credited with having differentiated a saccharine and a non-saccharine variety, but it remained for Johann Peter

Frank, in 1794, to first definitely recognize that there were two distinct forms of the disease. In one the urine possessed a honey-like taste, *diabetes mellitus*, or *verus*, in the other the urine had an insipid taste, *diabetes insipidus*, or *spurius*. Frank, first gave us a definition of diabetes insipidus, when he described it as a long-continued, abnormally increased secretion of non-saccharine urine which is not caused by a diseased condition of the kidneys. A better definition could hardly be devised for the present day.

Robert Willis, in 1838, proposed a classification of diabetes insipidus cases according to the urea excretion. *hydruria* included those cases where there was polyuria and a normal urea output, *azoturia*, those with polyuria and increased urea excretion; *anasoturia*, those with polyuria and diminished urea elimination. Subsequent experience showed that these did not represent distinct types of the disease.

From 1849, when Claude Bernard published the results of his famous piqure experiments on the medulla of animals, the investigation of the cause of diabetes insipidus entered the experimental stage. His so-called diabetic center is situated in the floor of the fourth ventricle near the tip of the calamus scriptorius and between the centers of the pneumogastric and aud-

*From the Department of Internal Medicine, Johns Hopkins University.

†Presented at the Baltimore meeting of the American College of Physicians, March 26, 1931.

itory nerves Puncture of this center in dogs caused a glycosuria Puncture at a point a little lower caused a polyuria, whereas punctures at a point a trifle higher in a frontal direction, he claimed, produced an albuminuria

Eckard, of Giessen, in 1870, confirmed Claude Bernard's findings and stated that there were other areas of the brain, injury of which in animals produced a transitory or permanent polyuria Kahler, writing about the same time, came to similar conclusions

In 1905, Eric Meyer advanced the view that diabetes insipidus was due to the inability of the kidneys to concentrate urine In order to dilute the serum of the blood so that the contained sodium chloride and nitrogenous products could be excreted by the kidneys, the patient was forced to drink more water, which led secondarily to an increased output of urine This theory received some support but was soon abandoned, for it was shown later by various investigators that the kidneys of patients with this disease were capable of eliminating a concentrated urine, that is, a urine with a specific gravity approaching the normal

Since 1910, there has been a very active investigation of the cause of diabetes insipidus The following three views, in succession, have been advanced

(1) That it is caused by disturbed function of the posterior lobe of the hypophysis

(2) That it is produced by organic changes involving one or more of the structures comprising the hypothalamus, and

(3) That there is a center, the *nucleus supraopticus* or *nucleus para-*

ventricularis located in the hypothalamus near the floor of the third ventricle, that presides over normal water metabolism, that nerve fibres originate in this center and pass down through the hypothalamus and infundibular stalk and spread throughout the entire posterior lobe and even between the cells of the pars intermedia, and that a lesion involving any part of this tract, the *tractus supraoptico-hypophysicus*, may so disturb water regulation that diabetes insipidus results

THE HYPOPHYSIS CONCEPTION

A brief review of the functions of the various parts of the hypophysis is important in a consideration of its possible relationship to the etiology of diabetes insipidus It consists essentially of the anterior lobe, the posterior lobe or pars nervosa, and the pars intermedia, an epithelial envelope which partially surrounds the posterior lobe

The anterior lobe is a glandular structure, of ectodermic origin, and derived from Rathke's pouch Its two chief functions are concerned with growth and the development of sex characteristics We are not concerned with the activity of the anterior lobe in this discussion

The true function of the pars intermedia still remains a debatable question

The posterior lobe is of nervous origin, and, until recently, has been thought to consist essentially of neuroglia cells and fibers The recent work concerning the histology of this lobe will be deferred for a later discussion At its upper portion it is connected with the mid-brain, or hypothalamus, by the infundibular stalk.

The chief actions attributable to the extract of the posterior lobe of the hypophysis are its pressor, diuretic-antidiuretic, oxytocic, and melanophore-expanding properties. Whether these actions are due to a single substance or to one or more different products still remains a disputed question. Abel and his associates claim to have produced all these actions from the pituitary tartrate they have isolated from the posterior lobe. On the other hand, Kamm, Grote, Rowe and Bugbee have isolated two factors, vasopressin, which exerts the pressor effect, and oxytocin, which causes contraction of smooth muscle. Gargle, Gilligan and Blumgart have shown that the antidiuretic effect is linked up with the vasopressin factor.

For several years following 1910, the theory that diabetes insipidus was dependent upon lesions of the hypophysis held sway. Only a brief reference to some of the evidence supporting this conception can be given. In 1910 Harvey Cushing, in reporting the results on the removal of the posterior lobe in dogs, found that this operation was often followed by a transitory polyuria.

In 1913 Cushing, in his Shattuck lecture, stated that in his first 100 cases of pituitary disease polyuria had been so marked in six cases that it had led to a diagnosis of diabetes insipidus by the physicians referring the patients.

The first clinical report showing a relationship between diabetes insipidus and lesions of the hypophysis was made in 1912 by E. Frank. He reported a case in a man who had been shot and x-rays revealed the fact that the bullet was lodged in the sella turcica.

In the following year, 1913, M. Simmonds reported a case of diabetes insipidus in a woman, aged thirty-seven. Two months after an excision of the breast for carcinoma she developed a marked polyuria and polydipsia. The autopsy showed, in addition to numerous other metastases, one involving and destroying the posterior lobe of the hypophysis. The metastasis pressed on the pars intermedia but did not involve it or the anterior lobe.

Following these two reports numerous similar cases soon began to appear in the literature, apparently confirming this relationship.

An additional support was given to the posterior lobe conception by the appearance of reports in 1913 by von den Velden and Farini, working independently, that the hypodermic injection of pituitrin had a marked effect in reducing the polyuria and polydipsia in this disease.

As a result of the above evidence, it was natural that the view that diabetes insipidus was due to disturbed function of the posterior hypophysial lobe should have gained rather general acceptance.

THE HYPOTHALAMIC CONCEPTION

While the hypophysial idea of the cause of diabetes insipidus was gaining ground, some experimental work appeared casting doubt on it, and indicating that the lesion was not in the posterior lobe but in the hypothalamus.

The hypothalamus, or mid-brain, forms the floor of the third ventricle. It consists essentially, from before backwards, of the optic chiasm, the tuber cinereum, and corpora mamillaria. In addition there is the infundibulum.

ulum, situated below the tuber cinereum and terminating in the infundibular stalk, which is attached to the upper surface of the posterior lobe of the hypophysis

The question of the relationship between polyuria and experimental lesions of the hypothalamus in dogs was first undertaken by Camus and Roussy in 1913. They reported that they had been able to produce transitory polyuria by puncturing the hypothalamus of dogs through the sphenoidal bone with a heated drill. In one dog a permanent polyuria, as well as a dystrophia adiposogenitalis, resulted. They believed that it was injury to the tuber cinereum that produced the polyuria.

These investigators continued their experiments, and in 1920 reported what seemed rather convincing evidence that the polyuria does not depend on a lesion of the posterior hypophysial lobe, by producing it in a dog from which the hypophysis had been previously removed. The investigations of Aschner, and of Houssay and Hug supported the findings of Camus and Roussy.

Bailey and Bremer, in 1921, reported from Cushing's Clinic a very careful piece of experimental work on dogs confirming the views of Camus and Roussy. With the technique used by the latter there was always risk of injury to the pituitary. By a special surgical technique Bailey and Bremer exposed the hypothalamus by the temporal route, which permitted an exposure of the whole region. The punctures of the hypothalamus could be made where desired, and the pituitary, being in plain view, could be carefully avoided. When the animals died or

were sacrificed sections were made of the injured hypothalamus, and of the pituitary to make sure that the latter had not been damaged in the operation. In all of their thirteen dogs in which the hypothalamic puncture was performed there developed a polyuria which appeared in the first two days. According to the extent of the lesion it varied from a transient one, lasting from six to eight days, to an apparently permanent polyuria. It is interesting to note that in some of the dogs the physical effect of the puncture on the animals resembled that following hypophysectomy. Lesions of the tuber cinereum produced in two dogs a cachexia hypophyseopriva with acute genital atrophy, and in two other dogs an insidiously developing adiposogenital dystrophy. The integrity of the pituitary was in each of these cases verified histologically. It is important to note that these researches confirmed the observations of Camus and Roussy to the effect that injury to the hypothalamus, in addition to causing polyuria, also, in some instances, resulted in the production of an adiposogenital syndrome, which has been supposed to be dependent on pituitary disturbance.

Camus and Roussy, as already stated, believed that the polyuria in experimental cases was dependent upon damage to the tuber cinereum. Richter has shown that in the rat a marked and permanent increase in water-intake and urine-output can be produced by a fine puncture made in the brain stem near the hypophysis. On the other hand Helen Bourquim produced polyuria in dogs by injuries to the corpora mammillaria.

From the clinical standpoint there was evidence that diabetes insipidus in man could be produced by hypothalamic lesions. Erdheim, of Vienna, in a publication appearing in 1904, appears to have been the first to suggest, as a result of clinical and pathological studies, that the polyurias associated with organic brain disease were actually dependent upon tumors or other lesions involving the hypothalamus. Another frequently quoted case is that of Lhermitte, published in 1922, in which diabetes insipidus developed in a case in which a syphilitic lesion involved both the tuber cinereum and infundibulum. Babonniex and Lhermitte, in 1925, reported another case of diabetes insipidus with syphilitic basilar meningitis, with lesions also involving the infundibulum and tuber cinereum. Verron reported a case following trauma, in which there was a circumscribed necrosis of the infundibulum.

In 1928 Elmer, Kedzierski and Scheps reported a case of diabetes insipidus in a patient with hypernephroma of the kidney with a metastasis in the hypothalamus. An embolus of hypernephroma cells had blocked an artery causing a necrosis of the tuber cinereum. The writer, in 1929, published the records of a case of diabetes insipidus in a man who had a primary carcinoma of the lung, with a metastasis about 1.5 cm in diameter involving the infundibulum and tuber cinereum, with an intact pituitary.

With these reported cases there seemed very conclusive evidence that diabetes insipidus could be produced clinically and experimentally by lesions involving the structures comprising the hypothalamus without any involve-

ment of the posterior hypophyseal lobe. The suspicion began to arise that when the clinical picture of diabetes insipidus occurred in growths involving the posterior lobe, as well as in the case of hypophyseal duct cysts, the cause of the polyuria and polydipsia was actually involvement of or pressure on the structures comprising the hypothalamus. In a similar way might be explained the intense thirst and polyuria that not infrequently follow the attempted surgical removal of basilar tumors in the region of the hypophysis.

THE TRACTUS SUPRAOPTICO-HYPHYSSEUS CONCEPTION

From the foregoing it will be seen that we have the hypophysis and the hypothalamus proponents of the cause of diabetes insipidus. In recent years the adherents of the hypothalamus conception have been getting rather the better of the argument. It now remains to present the evidence which tends to show that the adherents of both groups are right in their interpretation.

To clarify this point it is necessary to summarize the very important work that was published by Greving¹ and Pines² in 1926 concerning the histology of the posterior lobe of the hypophysis and of the hypothalamic region.

The posterior lobe of the hypophysis, embryologically, is of nervous origin and has until recently been supposed to be made up practically entirely of glia fibres and cells. The general impression has been that it contained no evidences of secretory cells, similar to those of the anterior lobe, which is a typical secretory gland. However, in 1927, Lewis and Lee³ showed that it actually contained groups of cells pro-

jecting inwards from the capsule, which sometimes have a tubulo-racemose arrangement in infants up to four years

The general belief has been that the posterior lobe contained no true nerve fibres or nerve cells. However, as far back as 1904, Berkley³ described and pictured nerve cells with one or more processes coming off from them. Dandy⁴, in 1913, reported on the external nerve supply of the pituitary. He found that it is derived from the carotid plexus of the sympathetic nervous system. These nerves follow the arteries supplying the various portions of the hypophysis, and he noted that very few went to the posterior lobe. No sections of the hypophysis itself were made to demonstrate whether or not nerve fibres could be demonstrated within the gland. Cajal, in 1911, was the first to demonstrate actual nerve fibres in the posterior lobe by his silver-reduction staining method. Nerve fibres in this lobe were later reported from Cushing's laboratory.

Greving¹ of Erlangen, and Pines² of Bechterew's laboratory in Leningrad, in studying the cause of diabetes insipidus, attacked the problem from the standpoint of determining whether there were any demonstrable nerve paths originating at any particular point in the hypothalamic region and communicating with the posterior lobe. Working apparently independently, they have made a contribution to this problem which appears to be of the very greatest importance. They made serial sections in an obliquely horizontal direction through the hypothalamus, hypophysial stalk and posterior lobe and stained the sections by the silver

method. Their results briefly are as follows. They find that at the nucleus supraopticus and nucleus paraventricularis, situated on each side of the median line near the floor of the third ventricle and adjacent to the optic chiasm, nerve fibres arise forming a definite bundle which passes down on each side near the tuber cinereum through the infundibulum and infundibular stalk into the posterior lobe, where they form an extensive network, and surround groups of cells which are thought to form the secretion of the pituitary lobe. Some of these fibres can also be traced between the cells of the pars intermedia. Greving calls this tract of nerve fibres beginning in the nucleus supraopticus and terminating in the posterior lobe the *tractus supraoptico-hypophyseus*. The belief is that the tract belongs to the vegetative nervous system. The tentative conception is that the nucleus supraopticus is the center that presides over the normal regulation of water balance. The fact that this center is connected by a definite bundle of fibres with the posterior lobe, the extract of which has such a potent effect in relieving the polyuria of many cases of diabetes insipidus seems to be of the greatest significance. Cushing, in his Lister lecture of 1930 emphasizes the importance of the work of Greving and Pines, and seems to accept the view that there is a water regulatory center, the nucleus supraopticus. In referring to the work of these investigators he says, "When successfully stained, however non-myelinated nerve fibres in abundance at first can be traced from both the supraoptic and paraventricular nuclei (though more particularly from the

former) to converge at the infundibulum, whence in a compact bundle they pass down the pituitary stalk to enter the posterior lobe. Arrived there, they not only ramify widely throughout the pars nervosa weaving themselves as Greving states, in 'basket-like' fashion around what appear to be secretory islands, but they also, according to Pines, can be traced in among the epithelial cells of the pars intermedia."

The existence of this tractus supraoptico-hypophyseus, as described particularly by Greving, renders it probable that diabetes insipidus may result from lesions anywhere along its course, as suggested by Zadek.⁷ What relation this tract has with the cause of dystrophia adiposogenitalis has not been definitely settled. Greving suggests strongly such an association. Clinically, we not infrequently find a combination of diabetes insipidus and adiposogenital dystrophy. In the polyuria produced experimentally in animals, both Camus and Roussy, and Bailey and Bremer reported that in some instances the animals manifested both diabetes insipidus and also dystrophia adiposogenitalis. It is probable that the tractus supraoptico-hypophyseus was severed in these experiments. That a disturbance in the continuity of this tract may produce both conditions was reported by Cushing in his Cameron Lectures in 1925. He and Maddox, by placing a silver clip on the hypophysial stalk of dogs, after shrinking the brain by Weed's method so as to prevent damage to the mid-brain and hypophysis, produced both polyuria and dystrophia adiposogenitalis in the animal.

The discovery of the tractus supraoptico-hypophyseus goes a long way

towards reconciling the conflicting views of the pituitary and hypothalamic adherents. We can conjecture that it may be found that tumors or other lesions involving the nucleus supraopticus, the posterior lobe of the hypophysis, or of the tract anywhere between these points may produce diabetes insipidus.

TREATMENT

Only a brief reference to the treatment of diabetes insipidus can be made. If the patient has a positive Wassermann antiluetic treatment should be instituted, as the polyuria might be dependent upon a gumma of the mid-brain or upon a basilar syphilitic meningitis.

Surgical interference is often indicated where there are neighborhood pressure symptoms, such as headaches, ocular palsies, bitemporal hemianopsia, and choked discs. An early operation may prevent total blindness, even though it may not materially influence the polyuria.

The hypodermic use of 0.5 to 1 cc of surgical pituitrin often relieves the distressing thirst and polyuria. The dosage and interval between doses has to be worked out in each individual case. Usually the effect of an individual dose does not last longer than from four to six hours. Following basilar tumor operations, a distressing diabetes insipidus may develop when it did not previously exist. Frequently this polyuria and polydipsia will spontaneously disappear. If it does not, pituitrin therapy is indicated. The cause of the diabetes insipidus in these cases is probably due to damage to the supraoptico-hypophyseus tract during the operation.

Blumgart has found that the nasal administration of pituitrin is sometimes effective. A tampon of cotton soaked with pituitrin may be inserted into one nostril, or 1 cc of pituitrin may be diluted with 30 cc of normal salt solution and frequently sprayed into the nostrils.

In some instances it is found that pituitrin has little or no effect. Elmer, Kedzierski and Scheps⁸ have proposed a classification of diabetes insipidus from an etiological and therapeutic standpoint. It is as follows:

(a) Cases due to destruction of the posterior lobe of the hypophysis. Here the posterior lobe extract fails entirely or only in part to sensitize the regulating centers for water and salt in the hypothalamus. In these cases pituitrin has a definite, though transitory therapeutic effect, because the regulatory centers in the hypothalamus are intact.

(b) Cases due to destruction of the water and salt-regulatory centers in the hypothalamus. In these the secretion of the posterior lobe is still produced, but it cannot sensitize the hypothalamic centers because they are destroyed. In this group the pituitrin has no effect whatever, since the regulatory centers in the hypothalamus are destroyed and are incapable of sensitization.

(c) Cases in which there is an interruption of the communicating nerve fibres connecting the hypothalamus (tuber cinereum) and the posterior lobe of the hypophysis. This group, they state, is insufficiently understood and requires further investigation. The therapeutic effect of pituitrin is not stated.

If the views of these authors be correct, the failure of pituitrin to act therapeutically may be referred to those cases where the so-called center or centers are destroyed.

BIBLIOGRAPHY

- ¹GREYING, R. Anatomy and function of pituitary fibers connecting hypophysis and base of interbrain (Tr. supraoptico-hypophyseus), *Deutsch Ztschr f Nervenhe*, 1926, lxxxix, 179-195.
Klin Wchnschr, 1925, iv, 2181.
- ²PINES, I. L. Innervation of pituitary, *Ztschr f d ges Neurol u Psychiat*, 1925, c, 123-138.
- ³BERKLEY, H. J. The nerve elements of the pituitary gland, *Johns Hopkins Hosp Rep*, 1895, iv, 117-127.
- ⁴DANDY, W. E. The nerve supply to the pituitary body, *Am Jr Anat*, 1913-14, xv, 333-343.
- ⁵LEWIS, D., and LEE, F. C. The glandular elements in the posterior lobe of the human hypophysis, *Johns Hopkins Hosp Bull* 1927, xli, 241-277.
- ⁶CUSHING, H. Neurohypophyseal mechanisms from clinical standpoint (Lister memorial lecture), *Lancet*, ccvii, 1930, 119-127, 175-184.
- ⁷ZADEK, E. Die Beziehungen zwischen Anatomie und Klinik des Diabetes insipidus, *Ztschr f klin Med*, 1927, cv, 603-640.
- ⁸ELMER, A. W., KEDZIERSKI, J. and SCHEPS, M. Ein Fall von Diabetes insipidus verursacht durch eine Metastase eines Hypernephroms in Zwischenhirn. Beitrag zur Pathogenese des Diabetes insipidus. *Wien klin Wchnschr* 1928, xli, 591-594.

the burden represented by the weight loss. With very few exceptions, also, hunger disappeared within several days. When they found they could lose thus rapidly without hunger and with a feeling of increased energy, instead of lassitude, they were encouraged to continue and this contributed to the ultimate success obtained in these patients. The probable reason for these fortunate symptoms presents another contraindication to the use of thyroid in the treatment of obesity.

Patients on this dietary régime showed a more rapid reduction in the calories per hour oxygen exchange than in weight.⁷ The calories per hour of the patient presented above fell from 69 to 53, converting the basal metabolic rate calculated on her ideal weight from plus 25 at the beginning to minus 3 at the end of the dietary period. This is sufficient explanation for the increased resistance to fatigue and feeling of well-being these patients reported.

DuBois⁸, and Strang and McCluggage⁹ have shown that the rise in calories in response to a fixed meal—the specific dynamic action of the meal—is quantitatively the same in the obese and those of ideal weight if they are otherwise normal. Strang and McCluggage⁹ also presented evidence that the feeling of satiation after food comes from the attainment of the optimum rate of change of metabolism in response to it. With a fixed specific dynamic action this rate of change of metabolism is of course less in relation to a high basal metabolism than to a low one. In other words, it takes more food to give a feeling of satiation in a person with a high basal metabolic

rate than in one with a lower one, or conversely, the satiation from a fixed amount of food is greater with a low basal metabolic rate than with a higher. These observations related to the lowering of the basal rate of oxygen exchange observed in these patients probably accounts in part at least for their feeling of contentment with the food given.

If the drop of basal calories per hour oxygen exchange in these patients were prevented by thyroid medication, two worthwhile results now obtained probably would not occur. They would not have the increased resistance to fatigue and their appetites would not be as satisfied with the food given. They would, therefore, not feel so encouraged to continue and the ultimate results would probably not be as good.

THYROID MEDICATION INDICATED

While the 187 patients so far discussed were being successfully treated as described, four patients were found to whom thyroid administration was thought desirable because of a slow rate of weight loss. One woman who weighed 259 pounds was first seen after three months in bed because of another disability. Her calories per hour were 59, giving a basal metabolic rate of minus 26 for her actual weight and minus 8 for her ideal weight. After four weeks of dieting the calories per hour were 54, giving a basal rate for her actual weight of minus 34 and minus 18 for her ideal weight. The other three were young women in whom initial basal metabolic rates within normal limits early in the dieting period fell to levels somewhat

below that normal for their ideal weight. They all reacted well under thyroid therapy combined with the diet, but so controlled that caloric exchanges never higher than normal for their ideal weights were obtained. No doubt each one of these patients had hypothyroid tendencies, but if they did there was no demonstrable clinical evidence of it. This observation is important in showing that there is no clinical evidence other than the basal metabolic rate by which the very rare patient in whom thyroid medication may be used to advantage can be picked out from the large group in which it is contraindicated. In these its use should be controlled by frequent basal metabolic rate determinations because if pushed to high levels the same undesired results as those discussed above for the patients in whom its use is contraindicated would, no doubt, ensue.

CONCLUSIONS

I. Thyroid administration in the treatment of most cases of obesity is not necessary because

1. A diet consisting of one gram of protein and three-fifths of a gram of carbohydrate per kilogram of ideal weight, and no more than fifteen to twenty grams of fat, gives diets of from four hundred to six hundred calories on which these patients come down rapidly without thyroid

2. They may be maintained on these diets for months if necessary with nothing but improvement in their general condition.

II. Thyroid administration in the treatment of most cases of obesity is contraindicated because

1. The calories per hour oxygen exchange giving a normal basal metabolic rate when calculated on the actual weight, if related to the ideal weight, give a figure considerably higher than normal. This represents one of the physiological strains of obesity which should not be increased by thyroid therapy.

2. The drop in the basal metabolic rates with the institution of limited diets probably accounts for the feeling of well-being and increased resistance to fatigue observed by these patients and in part for the feeling of satiation with the lowered food intake which affords contentment with the diet prescribed. This encourages these patients to persist and should not be eliminated by thyroid medication.

III. A few patients—perhaps no more than two per cent of all—do not lose weight rapidly without thyroid medication. These cannot be differentiated from the others by history or physical findings. They may be recognized with assurance only by repeated basal metabolic determinations during the course of dieting.

REFERENCES

¹McCIUGAGE, H. B., BOOTH, GEORGE, and EVANS, FRANK A. Creatinine excretion in abnormal states of nutrition, *Am. Jr. Med. Sci.*, 1931, *class*, 349.

-STRANG, I. M., McCIUGAGE, H. P., and EVANS, FRANK A. The nitrogen balance during dietary correction of obesity, *Am. Jr. Med. Sci.*, 1931, *class*, 356.

- ³EVANS, FRANK A Some factors in metabolism of importance in obesity, *Proc Clin and Clin Assoc*, 1930, xlv, 76
- ⁴EVANS, FRANK A, and STRANG, J M A departure from the usual methods of treating obesity, *Am Jr Med Sci*, 1929, clxxvii, 339
- ⁵STRANG, J M, McCLUGAGE, H B, and EVANS, FRANK A Further studies in the dietary correction of obesity, *Am Jr Med Sci*, 1930, clxxix, 687
- ⁶MEANS, J H Basal metabolism in obesity, *Arch Int Med*, 1916, xvii, 704
- ⁷STRANG, J M, and EVANS, FRANK A The energy exchange in obesity, *Jr Clin Invest*, 1928, vi, 277
- ⁸Du Bois, EUGENE F Recent advances in the study of basal metabolism, *Jr Nutrit*, 1930, iii, 217
- ⁹STRANG, J M, and McCLUGAGE, H B The specific dynamic action of a mixed meal in abnormal nutritional states, *Am Jr Med Sci*, in print

The Many Sided Question of Protein In Nephritis*†

By W S McCANN, M D, F A C P, *Rochester, N Y*

IN THE practical management of patients with nephritis, regardless of the type, the question of the protein metabolism assumes a position of great importance. When one considers the varied rôles played by proteins in the body, the problem of controlling or modifying their behavior becomes one of great complexity. The catabolism of protein, giving rise to urea, sulphuric and phosphoric acids, must be limited to the capacities of damaged kidneys to excrete these substances. The anabolic demands for protein must not be overlooked, as physicians have been prone to do, because new protein synthesis is often urgently needed to replace that destroyed by "wear and tear" or lost during albuminuria, and to regenerate dwindling serum proteins which have come to play such an important part in the maintenance of the water balance of the body. So prevalent has been the idea that protein catabolism exerts deleterious effects upon the kidneys and vascular system that patients are seen not infrequently with "hunger edema" due to protein

starvation resulting from the severe and prolonged restriction of the protein of the diet, and states of less marked malnutrition from this cause are common. Physicians fall into the error of assuming that the sole means of reducing the catabolism of protein is that of reducing its intake, forgetting that the endogenous metabolism may remain high even though little protein is taken in the diet. It is important, therefore, that attention be called to other methods for reducing the catabolism of protein and of increasing its deposition in the body for the replacement of body proteins destroyed by the "wear and tear" of living in health or in disease, as well as protein lost during albuminuria.

The catabolism of protein in the nephritic patient is influenced by the same factors which operate in most other individuals. There is the so-called "wear and tear quota", which is heightened by "toxic destruction" in the presence of fevers of infectious origin such as those which frequently precede or accompany hemorrhagic nephritis. Furthermore, when the supplies of fat and carbohydrate are inadequate protein catabolism is increased, so that we say that fats and carbohydrates spare protein. Finally we have to consider what happens when a man consumes more protein than is

*From the Department of Medicine, School of Medicine and Dentistry of the University of Rochester and the Medical Clinic of the Strong Memorial Hospital and Rochester Municipal Hospital, Rochester, New York.

†Presented at the Baltimore meeting of the American College of Physicians, March 24, 1931.

required to cover the irreducible minimum of wear and tear on body proteins

A normal man, provided he were physically capable of ingesting an amount of protein sufficient to cover his energy requirement for rest in bed, would experience an acceleration of his total metabolism as the result of such ingestion so that 40 per cent more heat would be produced in his body than the food protein could furnish. The energy for this extra heat would be derived from his stores of carbohydrate and fat. Rubner and Lusk¹ have called this the "specific dynamic action" of protein. A normal man, fully grown, will quickly adjust the level of protein destruction to protein intake, so that he is in nitrogen balance, provided the total energy of the food is adequate. If he does what Sívén² did, namely, reduces his protein intake to lower and lower levels, his urinary nitrogen excretion will fall to a minimal level of 3 to 4 gm per diem at which nitrogen balance can be established. In order to do this he must consume proteins of high "biological quality" in the sense of Thomas³, that is, proteins which contain all the necessary amino-acids required for the synthesis of human body proteins. Larger amounts are required if the proteins consumed are deficient in this respect, as many of the vegetable proteins are.

If our previously normal man were to acquire typhoid fever or a streptococcal infection, nitrogen balance could no longer be established at a low level, or, in fact at a high level, unless the total calorie intake were raised to many times the resting energy requirement

as the work of Shaffer and Coleman has shown⁴. The difference between these two levels at which nitrogen balance could be established is the measure of the "toxic destruction of protein". Even in tuberculosis, which causes only a slight toxic destruction, the writer⁵ found that the minimal level of nitrogen balance could be reached only when the patients were able to take from two to two and one half times the number of calories required by the patient for rest in bed.

When toxic destruction ceases and convalescence begins the wasted body seizes upon food protein with avidity and replaces that destroyed, so that nitrogen excretion may remain low even when the intake is high. The same phenomenon follows periods of partial or complete starvation. Let us apply some of these considerations to the case of a young man with acute hemorrhagic nephritis. During the attack of scarlet fever or of tonsillitis which preceded or ushered in the nephritis, toxic destruction of protein occurred and will persist as long as the infection lasts. During this period increased amounts of the end products of protein catabolism will be produced no matter how low we reduce the protein intake. As water excretion is reduced these end products are retained and usually appear in increased amounts in the blood of such patients. If we reduce the salt intake and administer water the urine volume may increase to an amount adequate to sweep the blood clear of extra urea. In such cases it is usually possible to increase the intake of carbohydrates to a high level and in this way to dimin-

ish to some extent the abnormally high endogenous metabolism of protein

Edema will probably have occurred at first without low serum proteins. The urine will show increased amounts of serum albumin and serum globulin, fibrinogen, and hemoglobin, representing considerable losses to the body which should ultimately be replaced. The urinary globulin and the hematuria, as Van Slyke and coworkers have shown⁶, give us a fair measure of the intensity of the damage to the kidney. Prolonged loss of these substances diminishes their amount in the blood, producing anemia and reducing serum proteins. Years ago Starling⁷ showed that the balance between the osmotic pressure of the serum proteins and the hydrostatic pressure in the capillaries determines the escape and return of water to them. With the reduction of serum proteins the edema of our patient will tend to increase, particularly if the reduction affects chiefly the albumin fraction, which has a much greater swelling pressure than the globulin.

Experience has taught us that many cases similar to this one will undergo a transition along the following lines. The hematuria and urinary globulin will diminish greatly as the intensity of glomerular damage abates. Albuminuria and edema may increase until a clinical picture results which may closely simulate that of a primary degenerative nephritis or nephrosis, in which the predominating lesion is tubular degeneration. We have a suggestion as to how this comes about from the experiments of two of the younger workers in Christian's clinic. Barker and Kirk⁸, who depleted the serum

proteins of dogs by plasmapheresis and found that if this were continued tubular degeneration ensued.

Various workers have studied the regeneration of serum proteins after plasmapheresis. Kerr, Hurwitz and Whipple⁹, found that the regeneration period was shortest on a meat diet, longer on bread and milk, and longest during fasting, and that it was much prolonged when the liver was injured by chloroform or excluded by Eck fistula. Epstein¹⁰ sought to build up the serum proteins in nephrosis by giving high protein diets with considerable success. The writer, in unpublished experiments, has observed the effects of similar high protein diets on edematous patients with chronic hemorrhagic nephritis, the results of which may be summarized here. The patients invariably retained nitrogen, presumably as deposit protein, since non-protein nitrogen of the body fluids did not increase. Only a small fraction of the deposited protein appeared as circulating protein of the blood serum. The major portion of the deposit being outside the vascular system increased the water held in the tissues so that the weight increased and edema increased until the slowly increasing serum proteins reached the point at which increased diuresis and loss of edema could occur.

Before applying these results to other patients with hemorrhagic nephritis we should satisfy ourselves that the increase of protein in the ration will have no deleterious effects produced by disturbing the mechanism for acid-base balance or by possible renal damage by protein which the work of Newburgh¹¹ and others suggest.

For the maintenance of the acid-base balance the kidneys play a most important part. The non-volatile sulphuric and phosphoric acids resulting from protein catabolism are excreted largely by the kidneys, though partly through the bowel. When these acids pass through the kidneys normally *ammonia is formed by the kidneys* to accompany them, as shown by the work of Nash and Benedict¹¹. This normal ammonia formation prevents the loss of fixed bases and protects the alkaline reserve of the blood. In nephritis the mechanism fails in two ways. Retention of these non-volatile acids reduces the CO₂ combining power of the alkaline reserve. The ammonia forming function is frequently impaired in hemorrhagic nephritis. Observations made by Palmer and Henderson¹² in 1915 show clearly the reduced urinary ammonia of patients with renal acidosis. The failure of this function results in a drain upon the reserves of fixed bases which must accompany acids excreted in the urine, in the absence of adequate ammonia formation.

In the presence of renal damage sufficient to limit acid excretion or ammonia formation, an increase of protein in the diet is justifiable only when the catabolic processes can be limited and the anabolic augmented. Protein deposited makes no demand on the excretory mechanism or on the regulation of acid-base balance. Protein destroyed does make a great demand, but within limits this may be compensated for by increasing the basic constituents of the diet derived from fruits and vegetables or administered as the alkali-salts of citric or other organic acids. The problem of renal acidosis

presents a difficulty which is not insuperable.

Newburgh¹³ has raised an important question as to the possibilities of producing renal injury by protein in the diet. He was able to produce renal lesions in white rats, by feeding them diets consisting of as much as 75 per cent dried liver, casein, or beef muscle. Such liver feeding produced granular kidneys in less than a year. Casein produced tubular injury in 16 months, while beef muscle produced changes intermediate between the two. Looking at these results critically one is struck by the fact that a far greater proportion of protein was given to the rats than could possibly be taken by man, and also by the probability that the differences between the effects of the materials fed may depend upon substances associated with the simple proteins, possibly substances arising from nuclear material. Dr Newburgh has kindly permitted me to mention that further experiments of his, which will soon be published, indicate that the latter supposition is probably true. Substances like liver may produce renal injury if taken long enough and in sufficient amount. It remains to be shown that such injury occurs in man in the amounts which can ordinarily be taken.

On the other hand, we have the testimony of Stefansson as to the absence of injurious effects in the case of the Eskimo who gets 40 per cent of his energy from protein. McClellan and DuBois¹⁴, who recently completed a year of observation of Stefansson and Anderson on a meat-fat diet such as one may live on in the Arctic regions, found no demonstrable injury of

any kind Also McCay¹⁵ of the Indian Medical Service has testified that the incidence of nephritis is no greater among the meat eating Europeans in India than among the Bengali who get very little good protein

In the writer's clinic, Dr Henry Keutmann has carried out some very careful observations of the effect of high protein in the diet on the course of chronic hemorrhagic nephritis These observations are being published in detail elsewhere Patients were selected who had come to a fairly constant level of hematuria as measured by the Addis sediment counts¹⁶ In the following table are compared some of the observations made in a typical case of a boy of 15 years with chronic hematuria following upon an attack of acute nephritis, months before Comparison is made between the findings during two weeks on a diet containing 75 gm protein and during four weeks on a diet containing 150 gm

During the experiment the patient improved clinically, showed no elevation of blood pressure, maintained con-

stant weight and a positive nitrogen balance The relationship between the urinary ammonia and the total titratable acidity remained unchanged though both of these were increased 50 per cent when the protein intake was doubled

SUMMARY

These experiments have convinced us that liberal protein allowances in the diet do not of themselves, injure the kidneys When the excretory power is nearly at the level of the minimal endogenous protein catabolism which can be achieved by making full use of the protein sparing qualities of carbohydrate and fat, nothing is gained by reducing the protein intake below the point of nitrogen balance Full advantage should be taken of the tendency to deposit protein by all individuals who have lost it, either by inanition or by toxic destruction or through albuminuria Protein which is deposited makes no demand upon excretory functions, it builds up depleted tissue and circulating proteins with beneficial effects upon the course of the disease

TABLE I JULIUS B

	75 gm. Protein 14 days	150 gm Protein 28 days
N P N	26-41 mgm %	26-38
CO ₂ C P	57-60 vol %	55-74
Serum Proteins	7.2-7.4%	7.5-7.6
Urine pH	5.3-5.5	5.1-5.8
Urine R B C	122-310 ($\times 10^6$ per 12 hrs)	95-284
Urine Protein	Av 65 mgm (per 12 hrs)	Av 71 mgm
Casts 12 hr	150-697 ($\times 10^3$)	86-284
Urea Clearance	45-64 cc (C _u)	63-84 cc

REFERENCES

- ¹LUSK, GRAHAM The science of nutrition, 4th Ed, pp 276-318, 1928, Saunders, Philadelphia
- ²SNÍÉN, V O Ueber das Stickstoffgleichgewicht beim erwachsenen Menschen, Skand Arch fur Physiol, 1900, x, 91
- ³THOMAS, KARL Ueber die biologische Wertigkeit der Stickstoff Substanzen in verschiedenen Nahrungsmitteln, Arch f Physiol, 1909, p 219
- ⁴SHAFFER, P A, and COLEMAN W Protein metabolism in typhoid fever, Arch Int Med, 1909, iv, 538
- COLEMAN, W, and DuBois, E F The influence of the high caloric diet on the respiratory exchanges in typhoid fever, Arch Int Med, 1914, xiv, 168
- ⁵MCCANN, WM S The protein requirement in tuberculosis, Arch Int Med, 1922, xxix, 33
- ⁶VANSLYKE, D D, ET AL Observations on the courses of different types of Bright's disease, and on the resultant changes in renal anatomy, Medicine, 1930, ix, 257-386
- ⁷STARLING, E H On the absorption of fluid from connective tissue spaces, Jr Physiol, 1895, xix, 312
- ⁸BARKER, M H, and KIRK, E J Experimental edema (nephrosis) in dogs in relation to edema of renal origin in patients, Arch Int Med, 1930, xlv, 319
- ⁹KIRK, W J, HURWITZ, S H, and WHIPPLE, G H Regeneration of plasma proteins after plasmapheresis, Am Jr Physiol, 1918-19, xlvii, 356, 370, 379
- ¹⁰EPSTEIN, ALBERT A Further observations on the nature and treatment of chronic nephrosis, Am Jr Med Sci, 1922, clxiii, 167
- ¹¹NASH, THOMAS P JR, and BENEDICT, STANLEY R The ammonia content of the blood, and its bearing on the mechanism of acid neutralization in the animal organism, Jr Biol Chem, 1921, xlviii, 463
- ¹²PALMER, W W, and HENDERSON, L J On the several factors of acid excretion in nephritis, Jr Biol Chem, 1915, xxi, 37
- ¹³NEWBURGH, L H, and CURTIS, A C Production of renal injury in the white rat by the protein of the diet, Arch Int Med, 1928, xlii, 801
- ¹⁴MCCLELLAN, W S, and DuBois, E F Clinical calorimetry prolonged meat diets with study of kidney function and ketosis, Jr Biol Chem, 1930, lxxxvii, 651
- ¹⁵MCCAY Investigation of Bengal jail dietaries, Scientific Mem of India, 1910, No 37, 240
- ¹⁶ADDIS, THOMAS The number of formed elements in the urinary sediment of normal individuals, Jr Clin Invest, 1926, ii 409

Mountain Fever and Spotted Fever of the Rocky Mountains—Clinical Studies*

By NOXON TOOMEY, B A , M D , F A C P , *Palmyra, Mo*

UNKNOWN fevers first encountered by white immigrants in the Rocky Mountain region between 1850 and 1873 have become of constantly increasing clinical interest and public health moment due to recent discoveries of new and widened endemic areas, and to the involved medical problems now more fully appreciated.

Scientific study of fevers in the Rocky Mountain region began clinically in 1880, epidemiologically and pathologically in 1902, bacteriologically in 1906, immunologically in 1908, and preventively in 1911. These studies have so increased rather than narrowed the fields of inquiry that much of what has been written has had to be rewritten from time to time to accommodate the newer scientific facts and observations relative to the spread and increasing knowledge of this disease or these diseases. So great has been the enlargement of the public health and scientific relations of spotted fever and its congeners within the last four or five years that standard monographs of a few years ago give a very inadequate picture of the economic and medical problems as now known. Hence a comprehensive clinical study taking into account the newest sci-

tific facts can further perfect the literature of internal medicine.

Of the group of mountain fevers in the western part of the United States we will first consider the component of the group that is now the best known, namely spotted fever, although there is reason to believe that the non-exanthematous, intermittent tick-borne disease (mountain fever) was encountered by white men equally early or earlier than spotted fever. The early history of the intermittent or mountain fever is more obscure because, being non-exanthematous, it was more difficult to unequivocally distinguish it from the other prevailing fevers of the mountains such as malaria and the fevers of the enteroides group.

EARLY HISTORY OF SPOTTED FEVER

Occurring among the Shoshones, Flatheads and Nez Perce Indians of southern Idaho, western Montana, western Wyoming, northeastern Nevada, and northwestern Colorado prior to immigration by Caucasians, *spotted fever of the Rocky Mountains* first occasioned illness among white settlers in 1873. It was first observed by Dr H. Dressing near Paradise Valley, Humboldt County, Nevada in 1882 and five years later by Dr. Conaghan.

*Submitted for publication July 31, 1931.

of Corvallis, Montana In the same year, 1885, it was observed in Lake County, Colorado, and in 1886 in Mesa County, Colorado It has, however, only recently attracted notice in those counties although it has apparently occurred there from time to time¹⁶⁴.

Although at first variously diagnosed as 'black measles', cerebrospinal fever, dengue or typhus, from 1880 to 1895 it became apparent to the more observant physicians practicing in the heavily infested areas that they were confronted with an undescribed disease or group of diseases At that time a modicum of the local practitioners considered mountain fever as distinct from spotted fever, but as the former term was used more loosely than the latter it undoubtedly included some other fevers seen at high altitudes And yet despite admitted unskilled diagnoses and recognized looseness in the use of the term mountain fever, the idea persisted in the minds of some judicious observers that there was a mountain fever that was not spotted fever, malaria, nor typhoid fever That fever they considered to be very probably an independent infection

The prevailing idea of local medical opinion in Idaho, reached prior to 1893, became known to Captain Marshall W Wood, U. S. A., Post Surgeon of Boise Barracks, Idaho, who reported the current opinion to the Surgeon-General of the Army. On the latter's direction Capt Wood later obtained brief clinical descriptions of the spotted disease from eight general practitioners These reports were published in 1896 under the title "Spotted Fever

The first public discussion of spotted fever and mountain fever was by the Idaho State Medical Society at Boise, Idaho, in 1896 (discussion opened by Dr William C. Maxey), and by the Rocky Mountain Interstate Medical Association at Salt Lake City in July, 1897 Neither meeting gave rise to published accounts of the discussions⁴⁶

Clinical studies made by the Maxeys, father and son, and reported by the son, Dr Edward E. Maxey, characterized the main symptomatology of the indigenous spotted fever and served to emphasize that in southern Idaho the disease was more prevalent but not nearly so virulent as in western Montana²

Satisfied of the infectious nature of the new and imperfectly studied disease, the first act of the newly organized Montana State Board of Health was in 1901 when it commissioned L. B. Wilson and Wm. M. Chowning to make an epidemiological and pathological study of the indigenous disease, with particular reference to the virulent form in the Bitter Root Valley Wilson and Chowning in their reports remarked upon mild, febrile cases without an eruption and of unknown nature, but did not make a study of cases of the sort, nor express an opinion as to their nature⁸

The chief permanent results of Wilson's and Chowning's studies were to make the Bitter Root Valley form of spotted fever more widely known, more fully described clinically, and more scientifically established in that their epidemiological studies led them to focus attention on ticks as vectors of the disease, without, however, actually establishing the fact They described

a piroplasm which they thought they saw in the blood of patients with the virulent form of the spotted fever, and attached etiological significance to it. Later, however, C W Stiles and W W Welsh recognized these supposed intra-erythrocytic organisms as artefacts¹⁵

Wilson and Chowning's supposition in regard to a tick as vector of the spotted disease was confirmed experimentally by McCalla and Brereton who in 1905 transmitted the mild, Idaho type of spotted fever to man (two cases) and by King and Ricketts who transmitted the virulent Bitter Root Valley strain of the disease to guinea-pigs by means of tick attachment (feeding) experiments

The high mortality rate (70 to 90 per cent) and the economic importance of the malignant Bitter Root Valley form of spotted fever so centered the attention of investigators on it that the benign, aberrant and non-exanthematic forms of local fever attracted almost no scientific study, with practically the sole exception of the mild form of spotted fever indigenous to the Snake River Valley in Idaho, which on account of its habitual low mortality rate (5 per cent) had from the earlier days led some to consider that it should be recognized as a separate disease. However, by means of later serologic studies the Idaho form of the disease has been proven to be immunologically identical with the malignant Bitter Root Valley form although amply warranting consideration as a distinct and easily recognizable clinical type due almost certainly to a fixed difference in the virulence of the local strain of the virus

As an historical account of the laboratory, and other scientific work done on these fevers since Ricketts first took up the problem in 1906, would have to do exclusively with the exanthematic or spotted fevers peculiar to the Rocky Mountain area, an account of the discoveries connected with them will be deferred until after presenting a discussion of mountain fever

MOUNTAIN FEVER

Dismissing the fact that the term mountain fever has been used in almost all languages for whatever zymotic distemper may have prevailed at the time in the high altitudes of the region, it will for our purpose be sufficient to note that the fever under discussion is not implied to have any relationship with the mountain fevers of Europe, India, or any other part of the globe and is used only with respect to the medley of febrile diseases that have laid men low in the Rocky Mountain areas

As a popular sobriquet for plasmodium infection, *Eberthella typhi* infection, or one of the paratyphoid fevers (including tularemia and brucellosis), the term mountain fever has perhaps enjoyed most currency in the mountainous West. Connoting nothing to the medical mind, the use of such a term in medical literature is usually regarded as a token of ignorance. Nevertheless the term has a history and a persistency in the West and it is for us to determine if possible whether by it a separate disease entity has at times been designated

The earliest professional use in the West of the term mountain fever had to do largely with remittent and inter-

mittent fevers although by some the term was used for the continued fevers, including no doubt tularemia and abortive and masked forms of typhoid fever³. Although these reports were grouped by eastern bibliographers and clinicians with the aberrant forms of typhoid fever, the remittent and intermittent character of some of these mountain fevers stands out clearly. Also one is impressed by their comparatively short duration (eight to fourteen days), the seasonal incidence (April to June), the relation of *protracted chilliness but no chill* to fever, and the admitted *lack of effect of quinine* on them¹³. Furthermore, we know today that in some of the high mountain passes and valleys from which the "brief intermittent fever" was reported, plasmodium infection *must have been absent* in the early days as the necessary vector, an anopheline mosquito, *was not indigenous above the valleys of the plains*.

As in these cases no skin eruption was reported it would not conform to our present conception of spotted fever to regard them as being one and the same disease, nor cerebrospinal fever. That a focal infection (streptococcic or pyogenic), or bronchopulmonary invasion would explain all cases not due to a plasmodium or an enterococci, would seem most likely, and certainly some cases of tularemia would be confused with the doubtful group. Dengue or influenza perhaps accounted for the "epidemic mountain fever" mentioned by E. P. Vollum, and yet neither of those are apparently the endemic, seasonal, "brief remittents, easily cured" of the north Rocky Mountain region. A brucellosis (undulant fever) might

be the explanation of the mountain fevers of uncertain origin but if so it is extremely difficult to account for army cases being referred to as brief, for brief they must have been, because it is well known that in the army not only are men able to consult a doctor on the slightest pretext but do so to escape doing duty, hence it is unlikely that any of these army cases much exceeded two weeks, whereas brucellosis usually runs not under two to four months and usually longer; such a long protracted, low, ambulant fever would become known to the army medical officers in the West, and would have been described as such and not as "brief remittents easily cured". Furthermore we now know that mountain fever is tick borne and not milk borne, and is seasonal whereas brucellosis is not.

As for bronchopulmonary invasions accounting for these fevers of debatable nature we need have little concern as bronchitis, pleurisy and pneumonia in high altitudes are clear cut, particularly severe, diseases with localizing thoracic symptoms and signs so intense as not to escape the attention of a physician. It is therefore chiefly atypical plasmodial fevers, the focal infections and the zymotic infections of influenzal type that might give currency to an idea of mountain fever as being something apart from the previously recognized types of intermittent or remittent fever.

From none of the early literature on mountain fever in the West, after excluding cases of presumable plasmodium infection or the enterococci, can anything indisputably defensible from the standpoint of individuality be

tracted, as the focal infections or the zymotic infections of influenzal type can perhaps be invoked to explain the cause of the remaining undefinable cases. And yet through the maze of numerous early but unsatisfactory descriptions of non-exanthematic febrile cases in the Rocky Mountains, one catches glimpses of a brief remittent fever that does not conform to known forms of paludism, the fevers of focal origin, or influenzal attacks of gastrointestinal or upper respiratory tract type. This fever, after years of comparative study, was eventually characterized as follows: as being seasonal (limited to the spring and early summer months), as being of brief total duration with one to three forty-eight hour remissions with intermissions of two to eight days duration, with pronounced, prolonged chilliness at onset (which was fairly sudden) but without rigor, as being accompanied by constipation and severe muscle aches and pains (chiefly in the back and loins, with headache occasionally) and followed by a quick convalescence but a terminal anemia. Nothing was said about a skin eruption.

Mountain fever was observed to occur only in the spring and early summer months (tick season) and was categorically stated to be different from the autumn and winter fevers. It certainly was what the early practitioners in the mountainous portions of the West had in mind when they refused to ascribe to the eastern dictum that all mountain fevers were either malaria, typhoid fever, rheumatism (focal infections), cerebrospinal fever or influenza. As to the etiology and epidemiology of mountain fever nothing

was predicated, certainly ticks as vectors of the disease were not so much as suspected, although now known to be at least one of the vectors.

Due to limitations of space, only two extracts from the early literature will be given verbatim. One is an instructive tabulation of case incidence of mountain fever.¹¹ Despite the medley of fevers that were confused under the name 'mountain fever' the incidence of cases paralleling the tick season strongly suggests the occurrence of a special tick-borne disease. The second quotation is typical of many reports from army surgeons on duty at Wyoming, Montana and Utah military posts in the early days. This quotation is from the surgeon of a cavalry command of about five hundred men who were, in 1878, marched through the Wind River Canyon of Wyoming, one of the celebrated mountain fever and spotted fever areas of early as well as recent years. Although one man died of typhoid fever verified by necropsy, the bulk of the cases were acquired over a sixteen day period (four day bivouac and twelve day march through the mountains) at the end of which all were so nearly well as not to require hospitalization on reaching Fort Fetterman. Of these cases Doctor Gray wrote:

'These cases all presented the same general phenomena in the beginning. Invariably the first complaint was that of achings, aches and 'aching all over'. Then there was loss of appetite, thickly coated tongue and constipated bowels. The disease was in its full force ushered in with a well marked chill and during the first twenty-four hours the fever was always high. But there was mental obscurity, sometimes delirium, more or less during the subject's recovery. To cure whether they lived or died was

was done with or for them. The patient always admitted a feeling of distress, but never could localize it, except in one case (the man who subsequently died at Fort Fetterman, who complained greatly of pain in his head and the 'back of his neck'). The fever once developed, never after wholly left the patient, but exhibited a decided daily exacerbation, beginning with *chilliness* for a period of half an hour or so, accompanied by cold, clammy sweat, and followed by an intensely hot skin, with small and rapid pulse. These exacerbations generally continued about eight hours, sometimes longer, and then would follow a period of eight or ten hours of lower temperature and comparative freedom from discomfort, during which sleep was possible. There was an increasing, but not a great degree of prostration, as every man was able to ride his horse during the day's march of eighteen to twenty-five miles, and continued to do so daily without assistance until Fort Fetterman was reached. There were wanting the distinctive symptoms characteristic of typhoid, and yet quinia seemed to have no effect to prevent or control the daily return of the high fever, though administered in large doses."¹³

For a most valuable early account of mountain fever we have the report of Captain Charles Smart who strenuously tried to make mountain fever out to be malaria. By his own admission he had to write from Fort Bridger, Wyoming

'I could not bring myself to record these cases as malarial remittents but put them down as catarrhs and quincies, and awaited developments. These came in a very short time. Cases appeared of fever without any complication by local lesion, and I recognized that I must be dealing with the incipency of our so-called mountain fever."

He concludes a most careful description of three seasons' (Springs of 1874, 1875, 1876) experience with the so-called malarious, intermittent, tick-borne mountain fever, as follows

"One point, however, remains to be mentioned. It is that the records of the post, the figures left behind them by my predecessors as embodying their experience of the prevalence of mountain fever, corroborate my own observation, showing the months of May, June, and July to be the months of visitation. Thus, during the eight years previous to my assignment, May gave an average of 560 cases per thousand of mean strength, June, 1389, and July, 947, while no cases were recorded during the months of September and October. Yet Dr Drake reports those very months of September and October as the period of maximum prevalence of malarial fevers in the United States

The following table shows the average strength of the command and the prevalence of this fever in cases per thousand of mean strength —

Month	Strength	Cases
January	172	436
February	167	75
March	169	149
April	154	162
May	134	560
June	135	1389
July	132	947
August	145	426
September	131	
October	156	
November	171	585
December	168	74
Annual	153	4803

The same author writing of Camp Douglas, Salt Lake City, mentions three cases which "after being discharged from hospital as entirely recovered, made his [their] appearance in eight days with a recurrence of the febrile attack, but it was readily removed by quinia and no subsequent relapse has taken place"

The first account of the non-exanthematous, intermittent tick-borne (mountain) fever that has come to my notice is the following which was writ

ten by Assistant Surgeon Patzki at Fort Steele, Wyoming Territory, in 1875, and is as follows

"A remittent fever, occasionally very severe, is met with, by the mountaineers called mountain fever, and much dreaded by them. The most prominent symptoms are headache, severe aching through the whole body, insomnia, furred tongue, frequent full pulse, constipation. Chills are infrequent. The efficacy of large doses of quinine proves the malarial origin. The mountaineers treat it with their panacea, sage tea, and, as they assert, quite successfully. Men cutting timber along the streams, mostly Danes and Swedes, suffer most from this fever."¹⁰

Before considering the modern writings on the subject of mountain fever we will review the scientific work done on its 'family relation', or perhaps congener, spotted fever of the Rocky Mountains

THE RECENT HISTORY OF SPOTTED FEVER

From 1906 to 1911 the scientific work of H. T. Ricketts, P. G. Heine-
mann, and associates contributed greatly to a knowledge of the virus, the factors of transmission, the immunological reactions and the morbid anatomy of spotted fever. Later, in 1918, Wolbach added pathological and bacteriologic data and advanced as the causal virus a minute organism, a rickettsia which he was unable to cultivate except in tissue cultures.¹⁴⁶ Noguchi in 1923 was unable to confirm Wolbach's work but did show that three strains of rickettsia were non-pathogenic and that a filterable virus could be obtained from the vector, *Dermapentor andersoni*. Ricketts and Spencer and Parker were not successful in forcing the virus through a Berkefeld filter.²⁰¹

For our present purpose it is more important to note the tick control measures instituted by McClintock and Bishopp and augmented by Fricks, the tick parasites introduced and propagated in Montana by R. A. Cooley²⁰⁷, who has contributed valuable ecological studies of tick biology and distribution⁸⁶, the accurate statistics of spotted fever maintained by Dr. W. F. Cogswell, secretary of the Board of Health of Montana, and the epidemiological and parasitologic work of R. R. Spencer and R. R. Parker called forth by the spread of the disease since 1914.^{108, 114, 129} F. L. Kelly⁹⁸, J. G. Cumming¹⁰⁰, F. C. Stricker¹³¹, A. B. Tonkin²¹⁴ and particularly F. E. Becker^{164, 202} have studied spotted fever in its now more widely extended endemic area.

Lately (1931) Rumreich, Dyer and Badger have discovered an eastern and southeastern states endemic area that is believed to have been in existence for at least the past twenty years.²¹⁹

Spencer and Parker have introduced a practical vaccine of great preventive value.²⁰¹ Since 1925 between twenty to twenty-five thousand persons have been vaccinated with it.

Although the above mentioned studies were undertaken without reference to the non-exanthematic intermittent tick-borne (mountain) fever they constitute an invaluable foundation for future work on mountain fever.

MODERN OBSERVATIONS ON THE INTERMITTENT NON-EXANTHEMATIC TICK-BORNE (MOUNTAIN) FEVER

In 1896 from Fort Washburn, Wyoming Henry I. Ravenel described as typhoid fever a peculiar

of Rocky Mountain spotted fever and also non-exanthematic cases of two to four day fever with one remission lasting two or three days after an intermission of two or three days, and a short 6 to 8 day) total duration²⁹¹ Raymond was apparently unfamiliar with the medical ideas prevailing in Idaho and Montana with respect to spotted fever. His cases were all observed in the tick-season (late April to June) but as he finally regarded his cases as typhoid fever he incriminated the water supply and did not look for an insect vector. His case reports (Cases W S , J P , J F S , J C , F G W , and D A) leave no doubt that he observed cases of the intermittent, non-exanthematic tick-borne disease later described by Kieffer from a point in Wyoming some two hundred and fifty miles south-eastward. Raymond remarks on the prevailing divergence of opinion among the local practitioners, one of whom (Dr H L Callaway) clearly distinguished his typhoid fever cases from the spotted fever cases, which were then diagnosed as purpura simplex and purpura rheumatica (simplex).

In 1901 Dr W W Woodring of Mt Pleasant, Utah, before the Rocky Mountain Interstate Medical Association maintained "that there is such a thing as mountain fever, mostly confined to the young and those under fifty. It is ushered in with a chill followed by a temperature of one to four degrees during the following twenty-four hours." ¹ (Quoted from abstract in Jr Am Med Assoc.)

In 1902 Wilson and Chowning in writing of spotted fever, which they

suspected as being a tick-borne disease, state "Several physicians, however, recognize in addition a mild type in which there are no spots. There is much difficulty in the accurate diagnosis of the mild type, and though its existence must be recognized yet during the investigation herewith reported, all of the examinations except one were made on cases of severe type. In Montana cases of the mild type of the disease, which show no spots, are as yet too indefinitely differentiated to permit of their inclusion with those of the severe type which invariably develop the eruption. That such cases exist there can be no doubt. They are never fatal."

It is to the careful studies of Major Charles F Kieffer at Fort D A Russell, Wyoming, in 1906, that we are indebted for the first exact knowledge of an intermittent, non-exanthematic tick-borne disease of short duration and no known mortality. Kieffer prefaced his paper with the recognition that "the older physicians in the Rocky Mountain regions have always insisted that there was a special type of fever indigenous to this section of the country. This fever or, as it appears to me, group of fevers has been given various names, but principally that of mountain fever. The group has simply been dismissed in recent years, although many good observers still hold that there is a type of fever which is neither malaria nor typhoid."²⁵

Kieffer recognized two types, one having three to seven recurrences of forty-eight hours duration marked by forty-eight hour intermissions and "another type, but not so common, in

which after the initial chill the temperature rises ladder-like for two or three days. These cases have more marked prodromes or more marked abdominal symptoms (abdominal tenderness and enlargement of the spleen) and present a clinical picture which is, at first, extremely suggestive of typhoid fever." Kieffer's paper should be read in the original.

After Kieffer's contribution, mountain fever attracted only local interest in Colorado and the adjacent parts of Wyoming and Utah. No notice was taken of it in medical literature until 1926 when F. E. Becker said that "certain symptoms of malaise, not typical of Rocky Mountain spotted fever, frequently follow tick bites in Colorado. Evidence supports the view that they are due to the tick bite, and are not part of the clinical picture of Rocky Mountain spotted fever. Many micro-organisms other than *D. ticketti* are found in the ticks of Colorado."¹⁰⁴ In a later paper Becker says "An atypical infection following tick bite with characteristic constitutional symptoms, but without a skin eruption, is common in Colorado and is locally known as 'Colorado Tick Fever'. If this is an attenuated spotted fever, the definition of this disease must be modified to include cases without skin rash. Indolent ulcers frequently occur at the site of the tick bite."²⁰³

In 1929, R. R. Parker wrote "Public Health Service investigators have for several years been interested in a wood-tick-caused condition which occurs quite extensively in portions of Colorado and is far from uncommon in Wyoming. In sections of Colorado this

condition has been commonly known as 'mountain fever'. Compared to the usual typical cases of spotted fever it is relatively quite mild and at the present time it is uncertain whether it is a mild type of spotted fever or a distinct disease entity."¹⁹²

With respect to a Rocky Mountain spotted fever without an eruption, Dr. R. R. Parker in 1930 said " 'spotted fever without eruption', a diagnosis which we feel is purely presumptive and rarely justified" (Page 95-¹⁹¹).

From the title of a paper by Dr. F. E. Becker before the Boulder County (Colorado) Medical Society on May 8, 1930, on "Rocky Mountain Spotted Fever with Special Reference to Cases Without Rash," we gain the impression that Becker considers mountain fever and spotted fever to be the same disease but on what evidence we have been unable to learn.

SPIROCHETOSIS FROM ARCADIAN

In 1930 Burford Weller and G. M. Graham of Austin, Texas, described a group of three cases of a relapsing fever following infestation with the tick *Ornithodoros turicata* acquired by some youths when they explored a cave in the Colorado River Valley, Texas. An unidentified spirochete was found in the blood in all cases, and a similar organism was recovered from a rabbit inoculated through the abraded skin with a crushed tick and thereafter violently ill. Graham, who later visited the cave, was bitten and was ill with a relapsing type of fever; a spirochete being recovered from his blood.

Serious constitutional reactions following bites of *Ornithodoros turicata*

(A Duges) 1876 and *O talaja* (Guérin-Meneville) 1849, and *O coriaceus*, (C L Koch) 1844, have been known in Mexico for many decades⁸² For the present at least it is not thought proper to consider this argasid spirochetosis as identical with the non-exanthematic, intermittent tick-borne (mountain) fever of the northern Rockies, due to well marked differences in the vectors and the clinical courses of the diseases

DIFFERENTIATION OF THE TWO WOOD-TICK TRANSMITTED FEVERS OF THE ROCKY MOUNTAINS

Spotted fever is now recognized to follow more different clinical courses than the two classical types described prior to 1908^{4,31,41} However, this fact is not accorded sufficient notice in textbook and clinical literature Up to 1908 the two recognized types were the *benign (very slightly remitting) type in Idaho*, and the *short but malignant form in the Bitter Root Valley*, the latter (usually without remissions) running a constantly rising febrile course to hyperpyrexia and ending almost invariably in circulatory collapse between the fifth to eleventh day

A *very mild, ambulant type* with exanthem scanty or evanescent is now not infrequently recognized in Idaho and eastern Oregon It is said to run a prolonged course (between three and a half to four weeks)

A *moderately severe, protracted, severely emaciating type* of the disease, in which the daily remissions are better marked than in other forms, occurs where the disease is of intermediate violence as in Nevada Utah, and

Colorado This type may last four to five weeks and is sometimes called the chronic type.

Inasmuch as there are four readily recognizable clinical types of spotted fever, the different strains of the virus will excite symptoms in somewhat differing intensity and combination Thus onset may be abrupt or more gradual (but is always reasonably clear cut and never very gradual) The fever may terminate with abrupt or gradual lysis but never by crisis The fever has a tendency to produce hyperhidrosis early but a dry skin later in the course, but the degree of hyperhidrosis is, as with certain other symptoms and signs, somewhat conditioned by the patient's habitus During onset, vomiting occurs commonly in the types of moderate and severe intensity, but like some other symptoms is partly conditioned by the patient's habitus, thus occurring in some of the mildest cases and not occurring in some of the most severe Universal chilliness, without rigor, varying in intensity from distinctly noticeable to marked, almost invariably occurs Usually the chill (chilliness) is not a shaking, chattering rigor but is more persistent than in other fevers, often lasting three to four hours, and is devoid of 'creepy feelings'.

Stupor is an early and rather constant characteristic of the disease, even in its mildest forms, and a low (only very exceptionally violent) delirium occurs commonly The tone of the muscles increases rather than lessens (a feature not sufficiently noticed in the literature). This may account for the spastic inability to void Constipation is usual during the first two or

three days. It seldom gives way to diarrhea. Inability to protrude the tongue and to speak are, in the severer forms, curiously frequent signs after the first few days. Insomnia is always a troublesome feature.

The pulse is characteristically quite rapid (110 to 140) becoming easily compressible in the virulent form. Respirations are normal or slightly more rapid, the respiratory excursion not being reversed. Very pronounced congestion of the conjunctivae without lachrymation is an almost constant symptom in all types of the disease. Muscle aches and pains, especially of the extremities, and chiefly of the flexor groups, occur early, practically at the onset, and may be one of the first symptoms.

The rash, occurring from the end of the second day to the fourth day, may be described briefly as consisting of erythematous (usually somewhat cyanotic) ovoid to pseudomorbiliiform, lenticular macules, at first slightly raised above the surface of the skin. The rash first appears on the ankles and wrist and spreads up the limbs to appear on the back and then the abdomen and chest, usually sparing the neck and face, which however commonly takes on a puffed appearance. The rash persists well into convalescence, usually becomes more or less purpuric, and stains from it may last for months. Confluence occurs in severe cases but is not common.

The fever of spotted fever is continued, slightly remitting in the milder cases, or constant to slightly rising in the malignant cases. At onset it usually rises abruptly or sub-abruptly with one

or two slight remissions during the first twenty-four hours. The fever may become distinctly remitting after the first few days, and especially quite so in the latter course of the moderately severe, protracted cases but never does it completely abate until the terminal lysis. However, without a distinct undulant type or definite intermissions there are occasional fluctuations in the daily maxima and minima. *Distinct intermittency does not occur in spotted fever* although after the abrupt lysis there may be, following a subnormal temperature for a day, an after-fever of very slight degree and of one or two days duration.

A severe secondary anemia develops after the first week of the disease, and persists well through convalescence, and small gangrenous areas on external genitals, ears, pharynx and sometimes on digits occur as not uncommon terminal complications in the protracted, severe forms.

As for *mountain fever*, with its equally abrupt onset. Besides the well marked intermittent character of the fever, and its brief total duration (eight to sixteen days), and the absence of an exanthem, *mountain fever* differs from *spotted fever* in its lack of local symptoms such as conjunctivitis, pharyngeal engorgement and terminal gangrenous areas. The site of the tick-bite is commonly the site of an indolent ulcer which is not the case in *spotted fever*. We note in both a stuporous state and pronounced aches and pains in the muscles but in *mountain fever* the latter are referred mostly to the back and loins whereas in *spotted fever* they are usually referred

extremities. Insomnia is a troublesome feature in spotted fever but occurs only transitorily or not at all in mountain fever. Constipation and urinary retention due to vesical spasm occur in both diseases, but bronchial irritation is not noted in connection with mountain fever. The pulse, quite rapid in both at the onset, has a very decidedly greater tendency to slowness, even to a distinct bradycardia, in mountain fever than in spotted fever, in which it has a tendency to become very rapid and thready, especially in the severe forms. Convalescence is much quicker and more rapidly completed, often being dramatic, after mountain fever than after spotted fever, which is usually quite protracted. Nothing like so great a secondary anemia is produced by mountain fever compared to the fifty per cent erythrocyte and hemoglobin reduction of spotted fever. The tongue is dry, furrowed and thickly coated from the onset of mountain fever whereas during the first week or ten days of spotted fever it is swollen, somewhat moist and only slightly coated. Drenching sweats seem to be a little more common during the remissions of mountain fever than during the abrupt lysis of spotted fever.

Although the clinical differences between mountain fever and spotted fever could be caused by a difference in the strain of the virus it is our opinion that unless the two diseases are proven to be due to the same virus we have to recognize such a decided dissimilarity in their symptomatology and clinical course as to justify us in regarding them as separate disease entities.

THE RELATIONSHIP OF SPOTTED FEVER AND MOUNTAIN FEVER

Not until the immunologic relations of one disease to the other have been established will we have a secure basis for uniting these diseases or recognizing them as etiologically separate entities. Clinical study has gone about as far as it can. From the present observational aspect, the intermittent, non-exanthematic tick-borne disease has only one thing in common with spotted fever and that is the fact that it can be transmitted by the same species of tick. So also can tick paralysis and tularemia be transmitted by *Dermacentor andersoni*, and yet it is patent that they are different diseases from spotted fever, etiologically as well as clinically. Thus the fact of a vector common to spotted fever and mountain fever should not compel us to group them together, except perhaps as an epidemiologic expedient. For statistical purposes it would be eminently unwise to consider them the same disease, and this after all is one of the most practical tests.

By what means mountain fever will be more intimately compared to spotted fever we can not now predict, as it is not a serious disease and is not attracting scientific study. What we should learn is whether or not those who have had the intermittent, non-exanthematic tick-borne disease are immune to spotted fever. Obviously it would not be prudent to use a strain of spotted fever more virulent than the Snake River strain for a tick feeding experiment on one who had mountain fever but was known not to have had spotted fever. There are other

methods for testing the relationship. Blood drawn during the height of the intermittent, non-exanthematic disease can be injected into guinea-pigs immune to spotted fever and into those susceptible to spotted fever, and into men who have had and who have not had spotted fever, provided the donor is known to be not syphilitic. To try to give the benign disease, mountain fever to one immune to spotted fever by means of a tick attachment (feeding) experiment would be inconclusive if only negative data were acquired, as it would be extremely difficult to prove that the ticks used were virulent for mountain fever at the time of the attachment. The virus does not occur in all wood-ticks and its successful transmission is influenced, perhaps by phases of latency or other conditions. If the non-exanthematic, intermittent tick-borne disease can be established in a laboratory animal it is important that it be done so that the virus can then be transported more readily and maintained for study with greater certainty and convenience.

SUMMARY

For seventy-five years many physicians practicing in certain parts of the mountainous West have recognized a brief, seasonal, non-exanthematic, remittent fever with certain characteristic symptoms and no known mortality, which they have considered indigenous to the locality and different from typhoid fever, malaria or other known diseases, although confused with malaria or typhoid fever by some.

The early published reports are not

absolutely conclusive but a review of them leaves the impression that there were early observed cases of a fever, called mountain fever, that conformed to our present knowledge of the disease, and remain inexplicable on the basis of a plasmodial, enteroidal or undulant infection.

A seasonal, non-exanthematic intermittent (occasionally continued) and intermittent fever of short duration and no known mortality, and conforming to the conception of mountain fever as understood in certain parts of the Rocky Mountain region was associated by Kieffer with a transmission by means of the bites of wood-ticks.

The virus of mountain fever has not been studied and the immunology of the disease with respect to spotted fever is not known.

The tick-borne non-exanthematic mountain fever has a clinical course characteristic and peculiar to itself and one not difficult to distinguish in the aggregate.

For clinical or statistical purposes it would be exceedingly unwise to identify mountain fever with spotted fever or undulant fever.

Until its course is identified or the immunological relationships of the disease are clearly established mountain fever should be considered to be a distinct disease entity.

Nosologically the tick-borne mountain fever resembles the dengue group of fevers somewhat more closely than the relapsing (spirochetal) fevers. The name American Mountain Tick-fever is proposed for it.

REFERENCES

(The numbers of the articles indicate the chronological sequence of the papers in a complete bibliography compiled by the author)

- ROCKY MOUNTAIN SPOTTED FEVER
- ¹SWEET, C L, SPRINGER, W D, COLLISTER, GEORGE, FAIRCHILD, R M, BOWERS, L C, DuBOIS, J K, FIGGINS, D W, and ZIPF, H (through CAPT. MARSHALL W WOOD, U S A) Spotted fever as reported from Idaho Report of the Surgeon-General, U S Army, for period ending July 1, 1896, Wash, D C, Govt Print O, 1896, pp 60-65
 - ²MAXEY, EDWARD E Some observations on the so-called spotted fever of Idaho, Med Sentinel, 1899, vii, 433-438
 - ⁴McCULLOUGH, G T Spotted fever, Med Sentinel, 1902, x, 225-228
 - ⁸WILSON, L B, and CHOWNING, WM M Report on the investigation of so-called spotted fever, 1st Bien Rep Montana St Bd Health, Helena, 1903, 26-91
 - ¹⁵STILES, CH WARDELL Preliminary report upon a zoological investigation into the cause, transmission, and source of the so-called spotted fever of the Rocky Mountains, Ann Rep Surg Gen, U S Pub Health and Mar Hosp Serv, Wash, D C, 1904, 362-363, and Pub Health Rpts, U S Pub Health and Mar Hosp Serv, 1904, xix, 1649-1650
 - ²¹SMITH, R M Tick fever, with report of case, Northwest Med, iii, 201-205
 - ³¹SPINLER, WM O Mountain or spotted fever as seen in Idaho and Eastern Oregon, Med Sentinel, 1905, xv, 532-537
 - ⁴¹ROBINSON, A A Rocky Mountain spotted fever, with report of a case, Med Rec, 1908, lxxiv, 913-922
 - ⁴PIARSE, R A Tick or Rocky Mountain spotted fever, Utah Med Jr (Denver Med Times), 1909, xxviii, 415
 - ⁴⁴MAXEY, ED E Rocky Mountain spotted (tick) fever, with special reference to causal [sic] factors, mortality and geographical distribution in Idaho, Med Sentinel, 1908, xvi, 666-678, discussion, 703-711
 - ⁴SWEET, C L, and SMITH, W F Clinical phases of Rocky Mountain spotted fever, Med Sentinel, 1908, xvi, 678-687.
 - ⁸⁶COOLEY, R A Notes on little known habits of the Rocky Mountain spotted fever tick (*Deimacentor venustus* Banks), Jr Econom Entomol, 1913, vi, 93-95
 - ⁹⁸KELLEY, F L Rocky Mountain spotted fever, its prevalence and distribution in Modoc and Lassen counties, California, a preliminary report, Calif St Jr Med, 1916, xiv, 407-409
 - ¹⁰¹CAMPBELL, A J Rocky Mountain spotted or tick fever, Colorado Med, 1916, viii, 209-213
 - ¹⁰⁸PARKER, R R, and WELLS, R W Some facts of importance concerning the Rocky Mountain spotted fever tick (*Deimacentor venustus* Banks) in Eastern Montana, 2d Bien Rep Montana St Bd Entomol, 1917, 45-56
 - ¹⁰⁹CUMMING, JAMES G Rocky Mountain spotted fever in California, Jr Infect Dis, 1917, xxi, 509-514.
 - ¹¹⁴PARKER, R R Some results of two years' investigations of the Rocky Mountain spotted fever tick in Eastern Montana Jr Econom Entomol, 1918, xi, 189-194
 - ¹²⁷PARKER, R R Maintenance of the virus of Rocky Mountain spotted fever in nature with particular reference to conditions in the Bitter Root Valley, Special Bull No 26, Montana St Bd Health, 1923, 33-40
 - ¹³⁴STRICKER, F C The prevalency and distribution of Rocky Mountain spotted fever in Oregon, Special Bull No 26, Montana St Bd Health, 1923, 18-20
 - ¹¹⁶WOLBACH, S B, PINKERTON, H and SCHILRSINGER, M J The cultivation of the organisms of Rocky Mountain spotted fever and typhus in tissue culture 5th Bien Rep Montana St Bd Entomol, 1924, 29-32
 - ¹⁵⁷BROWN, B, and MACFEE, G A fatal case of Rocky Mountain spotted fever, Cal and West Med, 1925, xxviii, 1177

- ¹⁶⁴BECKER, F E Investigations on Rocky Mountain spotted fever in Colorado, Jr Infect Dis, 1926, xxxix, 81-88
 - ¹⁹²PARKER, R R Rocky Mountain spotted (tick) fever, Bull Nevada St Bd Health, No 9, 1929, 3-17
 - ¹⁹⁸SPENCER, R R, and PARKER, R R Infection by other means than tick bites, Bull No 154, Hyg Lab, U S Pub Health Serv, 1930, 60-63
 - ²⁰¹PARKER, R R, and SPENCER, R R Results of four years' human vaccination, Bull No 154, Hyg Lab, U S Pub Health Serv, 1930, 72-103
 - ²⁰³BECKER, F E Tick borne diseases in Colorado, Colorado Med, 1930, xxvii, 36-44, 87-95
 - ²⁰⁷COOLEY, R A Review of tick parasite work for 1929 and 1930, 8th Bien Rep Montana St Bd Entomol, 1931, 16-25
 - ²⁰⁸KOHL, GLEN M A summary of parasite liberations, 8th Bien Rep Montana St Bd Entomol, 1931, 26-35
 - ²¹⁴TONKIN, A B Rocky Mountain spotted fever in Wyoming, Colorado Med, 1931, xxviii, 97-100
 - ²¹⁸DYER, R E, BADGER, L F, and RUMREICH, A Rocky Mountain spotted fever (Eastern type) Transmission by the American dog tick (*Dermacentor variabilis*), Pub Health Rep, U S, Pub Health Serv, 1931, xli, 1403-1413
 - ²¹⁹NEWS ITEMS IN JR AM MED ASSOC 1926, lxxxvii, 251-252, 1402, 1745, 1927, lxxxviii, 1649, lxxxix, 530, 1928, xc, 1049, 1223, cxi, 807, 1929, xcii, 731, 1605, xciii, 1229-1230, 1930, xciv, 799
- MOUNTAIN FEVER
- ³WAGGONER, F R On the mountain or continued miasmatic fever of Colorado territory, Am Jr Med Sci, 1850, N S 1, 50-55
 - ⁵BOYLE, C E On mountain fever, St Louis Med and Surg Jr, 1851, ix, 454-456, and Ohio Med and Surg Jr, 1851, iii, 528-530
 - ⁶OATMAN, J E Mountain and malarious fevers produced by the same cause, Boston Med and Surg Jr, 1851, xlv, 511-512, and Northwest Med and Surg Jr, 1851, viii, 105-108
 - ⁷EWING, W T Mountain fever, St Louis Med and Surg Jr, 1855, xiii, 109-116
 - ⁹PATZKI, Assistant Surgeon Sanitary Report, Fort Steele, Wyoming Territory Report on Hygiene of U S Army, 1975, p 385
 - ¹⁰TOWN, F L Sanitary Report, Fort Shaw, Montana Report on Hygiene of U S Army, 1875, p 434
 - ¹¹JAQUETTE, Assistant Surgeon Sanitary report, Fort Boise, Idaho Report on Hygiene of U S Army, 1875, p 460
 - ¹²SMART, CHARLES On mountain fever and malarious waters, Am Jr Med Sci 1878, lxxv, 17-43
 - ¹³HOFF, JOHN VAN R Typho-malarial fever, the so-called "Mountain Fever" of the Rocky Mountain region, Am Jr Med Sci, 1880, lxxix, 38-60
 - ¹⁴REBER, C T Mountain fever and malarious waters, swamp fever and marsh miasm, St Louis Med and Surg Jr, 1880, lxxxviii, 448-451
 - ¹⁶BESHOAR, M Mountain fever, Rocky Mount Med Rev, 1881, i, 328
 - ¹⁷—— Mountain fever and pneumonia Calif Med Jr, 1882, iii, 397, 433
 - ¹⁸NEWTON, R C A case of mountain fever, Phila Med Times, 1882, xiii, 7-9
 - ¹⁹THOMPSON, J E Mountain fever, St Louis Courier Med, 1884, xii, 208-207
 - ²⁰CURTIN, R G Rocky Mountain fever, Trans Am Climat Assoc, 1886, N Y, 1887, iii, 90-107, and N Y Med Jr 1887, xlv, 29-31
 - ²²HUBER, L The so-called mountain fever of Colorado and adjacent regions its description and treatment Med News 1897 lvi, 278-281
 - ²³TRACY, W Mountain fever, Inc and Register, 1899 xli, 75-78
 - ²⁴CAMPBELL, W A The identity of spotted and the severer forms of so called mountain fever Trans Colorado Med Soc 1892 27-220, and Medical News 1892 lxx, 470-482
 - ²⁵WORK, HENRY Mountain fever, The News, 1893 lxx 376-378
 - ²⁶ADAMS, W L Mountain fever, Medical News, 1895 xli, 185-186, 186-187, 187-188, 188-189, 189-190, 190-191, 191-192, 192-193, 193-194, 194-195, 195-196, 196-197, 197-198, 198-199, 199-200, 200-201, 201-202, 202-203, 203-204, 204-205, 205-206, 206-207, 207-208, 208-209, 209-210, 210-211, 211-212, 212-213, 213-214, 214-215, 215-216, 216-217, 217-218, 218-219, 219-220, 220-221, 221-222, 222-223, 223-224, 224-225, 225-226, 226-227, 227-228, 228-229, 229-230, 230-231, 231-232, 232-233, 233-234, 234-235, 235-236, 236-237, 237-238, 238-239, 239-240, 240-241, 241-242, 242-243, 243-244, 244-245, 245-246, 246-247, 247-248, 248-249, 249-250, 250-251, 251-252, 252-253, 253-254, 254-255, 255-256, 256-257, 257-258, 258-259, 259-260, 260-261, 261-262, 262-263, 263-264, 264-265, 265-266, 266-267, 267-268, 268-269, 269-270, 270-271, 271-272, 272-273, 273-274, 274-275, 275-276, 276-277, 277-278, 278-279, 279-280, 280-281, 281-282, 282-283, 283-284, 284-285, 285-286, 286-287, 287-288, 288-289, 289-290, 290-291, 291-292, 292-293, 293-294, 294-295, 295-296, 296-297, 297-298, 298-299, 299-300, 300-301, 301-302, 302-303, 303-304, 304-305, 305-306, 306-307, 307-308, 308-309, 309-310, 310-311, 311-312, 312-313, 313-314, 314-315, 315-316, 316-317, 317-318, 318-319, 319-320, 320-321, 321-322, 322-323, 323-324, 324-325, 325-326, 326-327, 327-328, 328-329, 329-330, 330-331, 331-332, 332-333, 333-334, 334-335, 335-336, 336-337, 337-338, 338-339, 339-340, 340-341, 341-342, 342-343, 343-344, 344-345, 345-346, 346-347, 347-348, 348-349, 349-350, 350-351, 351-352, 352-353, 353-354, 354-355, 355-356, 356-357, 357-358, 358-359, 359-360, 360-361, 361-362, 362-363, 363-364, 364-365, 365-366, 366-367, 367-368, 368-369, 369-370, 370-371, 371-372, 372-373, 373-374, 374-375, 375-376, 376-377, 377-378, 378-379, 379-380, 380-381, 381-382, 382-383, 383-384, 384-385, 385-386, 386-387, 387-388, 388-389, 389-390, 390-391, 391-392, 392-393, 393-394, 394-395, 395-396, 396-397, 397-398, 398-399, 399-400, 400-401, 401-402, 402-403, 403-404, 404-405, 405-406, 406-407, 407-408, 408-409, 409-410, 410-411, 411-412, 412-413, 413-414, 414-415, 415-416, 416-417, 417-418, 418-419, 419-420, 420-421, 421-422, 422-423, 423-424, 424-425, 425-426, 426-427, 427-428, 428-429, 429-430, 430-431, 431-432, 432-433, 433-434, 434-435, 435-436, 436-437, 437-438, 438-439, 439-440, 440-441, 441-442, 442-443, 443-444, 444-445, 445-446, 446-447, 447-448, 448-449, 449-450, 450-451, 451-452, 452-453, 453-454, 454-455, 455-456, 456-457, 457-458, 458-459, 459-460, 460-461, 461-462, 462-463, 463-464, 464-465, 465-466, 466-467, 467-468, 468-469, 469-470, 470-471, 471-472, 472-473, 473-474, 474-475, 475-476, 476-477, 477-478, 478-479, 479-480, 480-481, 481-482, 482-483, 483-484, 484-485, 485-486, 486-487, 487-488, 488-489, 489-490, 490-491, 491-492, 492-493, 493-494, 494-495, 495-496, 496-497, 497-498, 498-499, 499-500, 500-501, 501-502, 502-503, 503-504, 504-505, 505-506, 506-507, 507-508, 508-509, 509-510, 510-511, 511-512, 512-513, 513-514, 514-515, 515-516, 516-517, 517-518, 518-519, 519-520, 520-521, 521-522, 522-523, 523-524, 524-525, 525-526, 526-527, 527-528, 528-529, 529-530, 530-531, 531-532, 532-533, 533-534, 534-535, 535-536, 536-537, 537-538, 538-539, 539-540, 540-541, 541-542, 542-543, 543-544, 544-545, 545-546, 546-547, 547-548, 548-549, 549-550, 550-551, 551-552, 552-553, 553-554, 554-555, 555-556, 556-557, 557-558, 558-559, 559-560, 560-561, 561-562, 562-563, 563-564, 564-565, 565-566, 566-567, 567-568, 568-569, 569-570, 570-571, 571-572, 572-573, 573-574, 574-575, 575-576, 576-577, 577-578, 578-579, 579-580, 580-581, 581-582, 582-583, 583-584, 584-585, 585-586, 586-587, 587-588, 588-589, 589-590, 590-591, 591-592, 592-593, 593-594, 594-595, 595-596, 596-597, 597-598, 598-599, 599-600, 600-601, 601-602, 602-603, 603-604, 604-605, 605-606, 606-607, 607-608, 608-609, 609-610, 610-611, 611-612, 612-613, 613-614, 614-615, 615-616, 616-617, 617-618, 618-619, 619-620, 620-621, 621-622, 622-623, 623-624, 624-625, 625-626, 626-627, 627-628, 628-629, 629-630, 630-631, 631-632, 632-633, 633-634, 634-635, 635-636, 636-637, 637-638, 638-639, 639-640, 640-641, 641-642, 642-643, 643-644, 644-645, 645-646, 646-647, 647-648, 648-649, 649-650, 650-651, 651-652, 652-653, 653-654, 654-655, 655-656, 656-657, 657-658, 658-659, 659-660, 660-661, 661-662, 662-663, 663-664, 664-665, 665-666, 666-667, 667-668, 668-669, 669-670, 670-671, 671-672, 672-673, 673-674, 674-675, 675-676, 676-677, 677-678, 678-679, 679-680, 680-681, 681-682, 682-683, 683-684, 684-685, 685-686, 686-687, 687-688, 688-689, 689-690, 690-691, 691-692, 692-693, 693-694, 694-695, 695-696, 696-697, 697-698, 698-699, 699-700, 700-701, 701-702, 702-703, 703-704, 704-705, 705-706, 706-707, 707-708, 708-709, 709-710, 710-711, 711-712, 712-713, 713-714, 714-715, 715-716, 716-717, 717-718, 718-719, 719-720, 720-721, 721-722, 722-723, 723-724, 724-725, 725-726, 726-727, 727-728, 728-729, 729-730, 730-731, 731-732, 732-733, 733-734, 734-735, 735-736, 736-737, 737-738, 738-739, 739-740, 740-741, 741-742, 742-743, 743-744, 744-745, 745-746, 746-747, 747-748, 748-749, 749-750, 750-751, 751-752, 752-753, 753-754, 754-755, 755-756, 756-757, 757-758, 758-759, 759-760, 760-761, 761-762, 762-763, 763-764, 764-765, 765-766, 766-767, 767-768, 768-769, 769-770, 770-771, 771-772, 772-773, 773-774, 774-775, 775-776, 776-777, 777-778, 778-779, 779-780, 780-781, 781-782, 782-783, 783-784, 784-785, 785-786, 786-787, 787-788, 788-789, 789-790, 790-791, 791-792, 792-793, 793-794, 794-795, 795-796, 796-797, 797-798, 798-799, 799-800, 800-801, 801-802, 802-803, 803-804, 804-805, 805-806, 806-807, 807-808, 808-809, 809-810, 810-811, 811-812, 812-813, 813-814, 814-815, 815-816, 816-817, 817-818, 818-819, 819-820, 820-821, 821-822, 822-823, 823-824, 824-825, 825-826, 826-827, 827-828, 828-829, 829-830, 830-831, 831-832, 832-833, 833-834, 834-835, 835-836, 836-837, 837-838, 838-839, 839-840, 840-841, 841-842, 842-843, 843-844, 844-845, 845-846, 846-847, 847-848, 848-849, 849-850, 850-851, 851-852, 852-853, 853-854, 854-855, 855-856, 856-857, 857-858, 858-859, 859-860, 860-861, 861-862, 862-863, 863-864, 864-865, 865-866, 866-867, 867-868, 868-869, 869-870, 870-871, 871-872, 872-873, 873-874, 874-875, 875-876, 876-877, 877-878, 878-879, 879-880, 880-881, 881-882, 882-883, 883-884, 884-885, 885-886, 886-887, 887-888, 888-889, 889-890, 890-891, 891-892, 892-893, 893-894, 894-895, 895-896, 896-897, 897-898, 898-899, 899-900, 900-901, 901-902, 902-903, 903-904, 904-905, 905-906, 906-907, 907-908, 908-909, 909-910, 910-911, 911-912, 912-913, 913-914, 914-915, 915-916, 916-917, 917-918, 918-919, 919-920, 920-921, 921-922, 922-923, 923-924, 924-925, 925-926, 926-927, 927-928, 928-929, 929-930, 930-931, 931-932, 932-933, 933-934, 934-935, 935-936, 936-937, 937-938, 938-939, 939-940, 940-941, 941-942, 942-943, 943-944, 944-945, 945-946, 946-947, 947-948, 948-949, 949-950, 950-951, 951-952, 952-953, 953-954, 954-955, 955-956, 956-957, 957-958, 958-959, 959-960, 960-961, 961-962, 962-963, 963-964, 964-965, 965-966, 966-967, 967-968, 968-969, 969-970, 970-971, 971-972, 972-973, 973-974, 974-975, 975-976, 976-977, 977-978, 978-979, 979-980, 980-981, 981-982, 982-983, 983-984, 984-985, 985-986, 986-987, 987-988, 988-989, 989-990, 990-991, 991-992, 992-993, 993-994, 994-995, 995-996, 996-997, 997-998, 998-999, 999-1000, 1000-1001, 1001-1002, 1002-1003, 1003-1004, 1004-1005, 1005-1006, 1006-1007, 1007-1008, 1008-1009, 1009-1010, 1010-1011, 1011-1012, 1012-1013, 1013-1014, 1014-1015, 1015-1016, 1016-1017, 1017-1018, 1018-1019, 1019-1020, 1020-1021, 1021-1022, 1022-1023, 1023-1024, 1024-1025, 1025-1026, 1026-1027, 1027-1028, 1028-1029, 1029-1030, 1030-1031, 1031-1032, 1032-1033, 1033-1034, 1034-1035, 1035-1036, 1036-1037, 1037-1038, 1038-1039, 1039-1040, 1040-1041, 1041-1042, 1042-1043, 1043-1044, 1044-1045, 1045-1046, 1046-1047, 1047-1048, 1048-1049, 1049-1050, 1050-1051, 1051-1052, 1052-1053, 1053-1054, 1054-1055, 1055-1056, 1056-1057, 1057-1058, 1058-1059, 1059-1060, 1060-1061, 1061-1062, 1062-1063, 1063-1064, 1064-1065, 1065-1066, 1066-1067, 1067-1068, 1068-1069, 1069-1070, 1070-1071, 1071-1072, 1072-1073, 1073-1074, 1074-1075, 1075-1076, 1076-1077, 1077-1078, 1078-1079, 1079-1080, 1080-1081, 1081-1082, 1082-1083, 1083-1084, 1084-1085, 1085-1086, 1086-1087, 1087-1088, 1088-1089, 1089-1090, 1090-1091, 1091-1092, 1092-1093, 1093-1094, 1094-1095, 1095-1096, 1096-1097, 1097-1098, 1098-1099, 1099-1100, 1100-1101, 1101-1102, 1102-1103, 1103-1104, 1104-1105, 1105-1106, 1106-1107, 1107-1108, 1108-1109, 1109-1110, 1110-1111, 1111-1112, 1112-1113, 1113-1114, 1114-1115, 1115-1116, 1116-1117, 1117-1118, 1118-1119, 1119-1120, 1120-1121, 1121-1122, 1122-1123, 1123-1124, 1124-1125, 1125-1126, 1126-1127, 1127-1128, 1128-1129, 1129-1130, 1130-1131, 1131-1132, 1132-1133, 1133-1134, 1134-1135, 1135-1136, 1136-1137, 1137-1138, 1138-1139, 1139-1140, 1140-1141, 1141-1142, 1142-1143, 1143-1144, 1144-1145, 1145-1146, 1146-1147, 1147-1148, 1148-1149, 1149-1150, 1150-1151, 1151-1152, 1152-1153, 1153-1154, 1154-1155, 1155-1156, 1156-1157, 1157-1158, 1158-1159, 1159-1160, 1160-1161, 1161-1162, 1162-1163, 1163-1164, 1164-1165, 1165-1166, 1166-1167, 1167-1168, 1168-1169, 1169-1170, 1170-1171, 1171-1172, 1172-1173, 1173-1174, 1174-1175, 1175-1176, 1176-1177, 1177-1178, 1178-1179, 1179-1180, 1180-1181, 1181-1182, 1182-1183, 1183-1184, 1184-1185, 1185-1186, 1186-1187, 1187-1188, 1188-1189, 1189-1190, 1190-1191, 1191-1192, 1192-1193, 1193-1194, 1194-1195, 1195-1196, 1196-1197, 1197-1198, 1198-1199, 1199-1200, 1200-1201, 1201-1202, 1202-1203, 1203-1204, 1204-1205, 1205-1206, 1206-1207, 1207-1208, 1208-1209, 1209-1210, 1210-1211, 1211-1212, 1212-1213, 1213-1214, 1214-1215, 1215-1216, 1216-1217, 1217-1218, 1218-1219, 1219-1220, 1220-1221, 1221-1222, 1222-1223, 1223-1224, 1224-1225, 1225-1226, 1226-1227, 1227-1228, 1228-1229, 1229-1230, 1230-1231, 1231-1232, 1232-1233, 1233-1234, 1234-1235, 1235-1236, 1236-1237, 1237-1238, 1238-1239, 1239-1240, 1240-1241, 1241-1242, 1242-1243, 1243-1244, 1244-1245, 1245-1246, 1246-1247, 1247-1248, 1248-1249, 1249-1250, 1250-1251, 1251-1252, 1252-1253, 1253-1254, 1254-1255, 1255-1256, 1256-1257, 1257-1258, 1258-1259, 1259-1260, 1260-1261, 1261-1262, 1262-1263, 1263-1264, 1264-1265, 1265-1266, 1266-1267, 1267-1268, 1268-1269, 1269-1270, 1270-1271, 1271-1272, 1272-1273, 1273-1274, 1274-1275, 1275-1276, 1276-1277, 1277-1278, 1278-1279, 1279-1280, 1280-1281, 1281-1282, 1282-1283, 1283-1284, 1284-1285, 1285-1286, 1286-1287, 1287-1288, 1288-1289, 1289-1290, 1290-1291, 1291-1292, 1292-1293, 1293-1294, 1294-1295, 1295-1296, 1296-1297, 1297

²⁷WALKER, J M Mountain fever and its relation to typhoid, Trans Am Inst Homeop, 1897, 432-446

²⁸RAYMOND, E I A peculiar mountain fever, Med World, 1897, xv, 452

²⁹RAYMOND, H I Mountain fever, Am Jr Med Sci, 1898, cxv, 276-294

³⁰GEISENDORFER, J A Some peculiar forms of enteric fever, Med Sentinel, 1898, vi, 8-10

³²STUVER, E Mountain fever, Med News, 1899, lxxv, 577-581.

³¹ORMSBY, E A Bilious typhoid or mountain fever, Calif Med Jr, xx, 225-228

³⁴WOODRING, W W Mountain fever—so-called, Denver Med Times, 1902, June

³⁵MEADER Quoted by Weller and Graham, no publication located

ARGASID SPIROCHETOSIS

⁸²NUTTALL, G H F, Warburton, C, ET AL Ticks A monograph of the Ixodoidea, 1902, Cambridge Univ Press

⁸³WELLER, BURFORD, and GRAHAM, G M Relapsing fever from tick bite in Texas, Jr Am Med Assoc, 1930, xcv, 1834-1835

American Mountain Tick-Fever and Spotted Fever of the Rocky Mountains—Comparative Epidemiography*

By NOXON TOOMEY, M D, F A C P, *Palmyna, Mo*

PARALLEL study of mountain fever and spotted fever affords a most useful method for ascertaining their characteristics, for establishing comparisons and differentials between them, and for determining their respective positions in the social, economic and medical life of our times. Indeed, one might be led to take for granted that inasmuch as both diseases have the same arthropod vector, epidemiology, parasitology and prophylaxis would be identical for the two. Such is true to a large extent but as the diseases do not absolutely conform in the mechanics of their pathogenesis, it is important to compare them in a way that will visualize the differences in their pathodynamics. A common factor or foundation for the two diseases is found, but for each there is a separate superstructure indicating individuality. These differences reinforce our clinical observations concerning the dissimilar nature of spotted fever and American mountain tick-fever.

As very much more is known of spotted fever than of mountain fever it is not possible in the present state of our knowledge to compare the two

diseases in all respects. As it is important, however, to give the most complete picture possible of the epidemiology of spotted fever, important features of the latter will be discussed even when the comparable features of mountain fever are not known. Thus not only will spotted fever be made known more comprehensively but for the further study of mountain fever various suggestive viewpoints will be presented for elucidation.

EPIDEMIOLOGY

Spotted fever is not contagious nor inoculable from man to man by means of customary contacts. The virus can, however, penetrate the unbroken skin and has been known to do so under exceptional circumstances, such as in the handling of ticks in experimental work.^{1,2} Several laboratory workers have contracted the disease from handling infected material such as tick viscera, tick eggs and tick feces.³

Concerning the artificial inoculability of *mountain fever* no data is available. From the fact, however, that the virus does not have as great a latent or virulent immunity-producing phase as the spotted fever virus, and as *mountain fever* has been known to cause larger outbreaks than spotted fever,⁴

*Submitted for publication, July 31, 1931.

seems that the virus of mountain fever has a greater certainty of transmissibility through the skin than that of spotted fever

For neither disease do fomites need be taken into practical consideration although it is not impossible that active virus persists for some days in dead tick material, and that the latter can be spread by fomites under extremely exceptional circumstances

Distribution *Mountain fever* is limited to an area within that of the spotted fever tick-area. According to present knowledge the inference is justified that the distribution of mountain fever is conditioned by most factors influencing the distribution of spotted fever and also by a factor peculiar to itself

Spotted fever is known to occur in the mountain fever area but in that area it is not quite as prevalent as in other portions of the *D. andersoni* distribution area. Thus, along the axis extending diagonally from the center of the State of Washington southeastward to the southeast corner of Colorado, and for a hundred miles on either side, the spotted fever occurs far more preponderatingly over the northwest two-thirds of this area, whereas mountain fever is limited (approximately) to the southeastern one-third. That the difference is not due to a change in the type of one and the same disease is evident from the fact that spotted fever when it does occur in the southeastern portion is clinically quite distinguishable from mountain fever and is substantially true to its type as existing in the north-west part of its area. Although causing somewhat more violent febrile symptoms when occur-

ring in the southeastern portion of its area^{26,178}

Spotted fever occurs in a western, Rocky Mountain or major endemic area, a minor or eastern-southeastern states endemic area, and sporadically elsewhere

The eastern area is from the southern border of New York to the northern border of Florida and from the Atlantic coast line westward to the Appalachian mountains

The western endemic area includes the southeastern quarter of Washington¹⁸⁰, the eastern half of Oregon¹⁸¹, several counties on the northern and (north) eastern border of California¹⁸⁰, all of Idaho except the extreme northern tip, all of Montana^{13,185}, all of Wyoming¹³⁵, the northern half of Nevada²⁸, the northern four-fifths of Utah⁶⁰, and the western three-fifths of Colorado. A characteristic is the especial prevalence of the disease in certain localities (valleys) of the area

In the above described area mountain fever is definitely known to occur only in approximately the lower and somewhat eastern half, namely in Colorado, Utah, Nevada and Wyoming, although it seems to occur to a limited extent somewhat northwestward of the main endemic area, namely in the southern portion of Idaho and Oregon. However, the northern portion of the *D. andersoni* distribution area, namely Montana and the adjacent parts of Idaho and Washington have not been sufficiently investigated for mountain fever. Mountain fever has not been reported from the eastern-southeastern states endemic area of spotted fever

Recent Spread For *spotted fever* the area of known distribution has increased greatly since 1904, and particularly since 1914. It is indubitable that spotted fever has lately occurred for the first time in areas where medical men were sufficiently skilled to have recognized it had it occurred at an earlier date. For instance in

Montana, until 1914, infection was definitely known in but four counties, Missoula, Ravalli, and Granite, west of the continental divide, and in Carbon county, bordering Wyoming in the south portion of the eastern part of the state. It has now been reported from thirty-one counties in the eastern portion of Montana. It has spread to South Dakota (first reported case in 1915), to North Dakota (first reported case in 1919) and Nebraska (first reported case in 1931)²¹⁵

Maver and others have shown that spotted fever can be transmitted by ticks other than *D. andersoni*, and as ticks that bite man are widely distributed over the United States, Canada and Mexico it is not improbable that spotted fever will eventually have a wider area of distribution.

As ticks do not migrate for any appreciable distance the recent sudden spread of ticks containing virus is probably to be partly accounted for by interstate commerce in live-stock, particularly in sheep, to the wool of which ticks cling for several days before being killed by the sheep's grease. However it would not be correct to suppose that the spotted fever area has been widened solely through the agency of man (commerce, etc.) as the area has undoubtedly been widening slowly through the migration of infected rodents, by means of the rabbit-tick and the widening dissemination of infected tick eggs by natural means.

It is interesting that the spread of spotted fever to the plains areas of Montana and Wyoming has not (according to available reports) carried mountain fever with it, notwithstanding that the western half (particularly

the southwestern quarter) of Wyoming has for years been heavily infested with mountain fever. In fact, by comparing early reports with the present known distribution of mountain fever, *the area of mountain fever appears to have diminished in extent*. This has occurred in the more densely inhabited (cultivated) portions of Colorado and Wyoming, and partly in the Black Hills, and is undoubtedly to be accounted for by the clearing of underbrush and the other tick-eradicatory measures incidental to intensive farming, whereas the virus does not seem to be spread among rodents by the rabbit-tick.

Seasonal Characteristics. Both spotted fever and mountain fever are seasonal diseases being limited by the occurrence of predatory wood-ticks and dog-ticks in nature. The tick season is from the first warm days of spring (March) to somewhat after the maximum heat of summer (about the middle or end of July) although cases have been known to occur not uncommonly as late as September, and rarely at other times of the year. The majority of cases occur in April, May and June, especially in May. Obviously there is some variation from year to year according to climatic conditions and also the seasonal range varies for different localities according to their latitude, altitude and exposure to sun, wind and rain-fall.²¹⁶

Both spotted fever and mountain fever have been observed in rare instances during the cold weather of late winter (middle of December to end of February). This exceptional seasonal incidence can be accounted for by dwellings having become infested

with virulent ticks during the preceding summer or autumn. Hibernating through the winter, these ticks in the dwellings become stimulated to activity at a date earlier than usual by the dwellings becoming over-heated.

Climatic conditions as factors in tick prevalence are important as they operate directly on the life-cycle of the tick and on the pabulum that supports the tick⁸⁷. Thus moderate warmth with moderate moisture and protection from abundant sun glare are the optimum conditions for the wood-tick, any departure in either direction diminishing their prevalence.

Whether there is a distinct difference between the climatic requirements of mountain fever and spotted fever cannot be asserted with full assurance as too little is known of mountain fever, but such data as are at hand seem to indicate that mountain fever is found in a higher and drier climate than is spotted fever, and that it has a longer seasonal incidence (cases being observed not uncommonly in August and early September) which may mean that the virus of mountain fever is more resistant to heat or sunlight, or both, than that of spotted fever.

Geophysical Characteristics Formerly much significance was attached to spotted fever being particularly prevalent in certain deep, isolated mountain valleys characterized by a spring freshet or water-shed from the melting snows on the upper mountain reaches⁷⁰. These spring freshets serve to increase the prevalence of the disease by irrigating the underbrush in which the ticks hibernate and by washing the ticks down to the foot-hills. Sage-brush

of woods with underbrush that is fairly dry the greater part of the time, and shaded from constant direct sun glare can become heavily infested. Areas subjected to constant or periodically recurring strong wind currents are not so favorably situated for harboring heavy tick infestation as are the protected sides of the valleys, and this is why the protected sides of valleys are more morbidic than the exposed sides.

Relation to Flora For *spotted fever* the endemic area is not conditioned by the topographical distribution of a special plant or plant relationship, although underbrush, particularly sage-brush, seems especially agreeable to the wood-tick⁷⁴.

Mountain fever is much more prevalent in wooded areas than in sage-brush plains and may tentatively be said to be confined to the upper timber regions of mountain passes and canyons.

Relation to Fauna That *spotted fever* is indigenous to small rodents, particularly chipmunks, was confidently anticipated early in the study of the disease⁷², but the latest serologic work has shown that while it does occur naturally among wild rabbits, ground squirrels, woodchucks and probably other small rodents (which act as the natural reservoir), it is actually a rare disease among them, and usually benign. These animals become more or less healthy carriers and are largely responsible for maintaining the disease in nature. Hence rodent extermination is a necessary part of any plan for exterminating the disease. The large wild animals, elk, deer, and mountain goat, and the large domestic animal-

horse, cow, sheep and dog are immune¹¹²

That *mountain fever* is more especially related to the mountain goat and mountain rat than the gopher and wild rabbit populations has not been proven but seems likely from the character of the localities where it is most endemic

For both diseases, infection of man may occur at any time of the day or night, and is not especially favored by any part of the diurnal cycle

Age Incidence In sections where families live in infected districts there is no characteristic age incidence for either mountain fever or spotted fever. Actually, however, cases are far more common among adults than among children, and this is especially true for mountain fever. This difference in age incidence is largely due to increased exposure to wood-ticks by reason of the occupations of the adults which occasion them to enter the wooded mountain sides as trappers, rangers, surveyors, miners, lumbermen, etc.¹²¹

Sex Incidence Differences in exposure to ticks by reason of occupation result in many more cases occurring in men than in women. Cases in women are often caused by ticks brought home by the men and boys of the household.

Occupational Incidence *Spotted fever* occurs mostly among persons engaged in agricultural pursuits, and except under special conditions is most common in persons associated with the various phases of the live-stock industry, especially the handling of sheep. Cases also occur, however, among forest service employees, prospectors, hunters, and others whose occupation or the pursuit of pleasure or profit

takes them into tick-infested sections¹⁰⁵

Mountain fever is associated more decidedly with the timber industry, hunting and trapping in the mountains, and other mountain pursuits, and in this respect it differs distinctly from spotted fever. Among the early reports of army surgeons in the mountainous West, mountain fever was commonly referred to, whereas spotted fever was observed only rarely, and in certain circumscribed localities (Wind River Valley, Bitter Root Valley, etc.)

Economic Importance *Mountain fever* has no economic importance other than that which attaches to any benign fever of short duration. With *spotted fever*, however, it is vastly different. No one who is not in close contact with the spotted fever situation can appreciate the degree to which spotted fever is dreaded in the sections in which it is endemic. Before the commencement of the tick season many fertile mountain valleys become temporarily depopulated, most families moving out until after the middle of July. Naturally such hazards and necessity for inconvenience depress property values and hamper development. The mental worry to which tens of thousands of families are subjected each year during the tick season restricts the enjoyment of the opportunity for out-door life which constitutes one of the greatest natural assets of the Rocky Mountain region. Because of the far greater number of persons involved these considerations far outweigh the economic loss due to the actual occurrence of human cases. The latter is a serious concern, since, though recovery occurs there is a

or less protracted period of convalescence, often of several months, during which it is often impossible for the patient to resume his usual occupation¹⁸⁷

The marked prevalence of spotted fever among sheep herders and others concerned with range management of sheep is frequently a real problem for wool growers, and in some sections is a factor which merits and receives serious consideration^{91,104}

THE VIRUS IN NATURE

Reservoirs. Investigations in Montana have shown the following rodents to be susceptible to spotted fever: the Columbian ground squirrel, *Citellus columbianus*, the side striped squirrel, *Callospermophilus leucurus cneiascens*, the woodchuck, *Marmota flaviventris*, the pine squirrel, *Sciurus richardsoni*; the white bellied chipmunk, *Eutamias g. umbrinus*, the yellow bellied chipmunk, *Eutamias b. luteiventris*, the wood rat, *Neotoma microps*, the snowshoe rabbit, *Lepus harti*, the cottontail rabbit, *Sylvilagus nuttali*, the white tailed jack rabbit, *Lepus t. campestris*, the prairie dog, *Cynomys l. ludovicianus* (Ord), the badger *Taxidea taxus* (Schreber); and the weasel, *Putorius arizonensis*

Character of the Virus The virus of spotted fever has been described as having two phases, a non-virulent phase capable of producing immunity but incapable of producing clinical manifestations of infection, and a virulent phase that causes the clinical manifestations of spotted fever and also permanent (or a long lasting) immunity. This bi-phasic character of the virus is the probable explanation of

certain features of the disease that were for long inexplicable. However, the biodynamics of this character of the virus have not yet been elucidated. The virus of spotted fever does not pass through a Berkefeld filter.

The virus of *mountain fever* seems not to have any biphasic character. It possibly can be identified with the filter passing virus recovered from the wood-tick (*D. andersoni*) by Noguchi.

Virulence *Mountain fever* does not differ greatly in virulence from year to year or with respect to the locality where acquired. There are minor variations in the clinical course of the disease in different outbreaks and there are two main varieties of clinical type, the relapsing type and the typhoidal type. Several clinicians have, however, remarked upon the great similarity of all cases of American mountain tick-fever as observed in a given epidemic.

Spotted fever is unique in the fact that the virulence varies greatly in different localities but that the virulence of the infection in any locality is reasonably constant. The areas of greatest known virulence are the west side of the Bitter Root Valley in western Montana, a small section on Kirby Creek near Thermopolis, in Hot Springs County, Wyoming, and an area in the Wind River mountains in Fremont County, Wyoming. In these sections the mortality is high, not infrequently reaching 80 to 100 per cent. The area of mildest infection is in the Snake River Valley in southern Idaho where the mortality seldom exceeds five per cent. Areas of intermediate severity occur in other sections of the Rocky Mountain region. Ambulatory cases

are not uncommon in southern Idaho and eastern Oregon¹⁸⁷

Mechanics of Transmission For both mountain fever and spotted fever the method of transmission is grossly the same, namely a fixation (bite) of a virulent tick in the human skin for the purpose of engorgement. In the instance of both diseases the virus is transmitted not mechanically, or by the feces, but in the suctorial juices inoculated by the tick during the process of engorgement. There are, however, slight time differences between spotted fever and mountain fever. In spotted fever the tick, even though potent with a highly virulent strain of spotted fever, does not become infective under one and three-quarter hours of fixation. The high proportion of non-immunes infected during certain epidemics (from one-fourth to one-half) leads to the inference that so long a time for infectivity to develop is not present in mountain fever.

ACTUAL AND POSSIBLE VECTORS

Spotted fever is known to be transmissible to man by means of the following species of ticks: the western wood tick *Dermacentor andersoni*, Stiles, 1908¹⁵², the California tick, *Dermacentor occidentalis*, Marx, in Utah by *Painapocetus magnatus*, by *Dermacentor albipictus*, Packard, in the northern plains by *Amblyomma americanum* (Linnaeus), and in the eastern-southeastern states by the dog-tick, *Dermacentor variabilis* (Say). Banks, 1908. These ticks also feed on small rodents. No infected *D. albipictus* have been recovered from nature in spite of repeated tests.

Haemaphysalis leporis - palustris Packard, a rabbit-tick, feeds on all species of rabbits and on game birds but is known not to feed on man. It is, however, a potent and very serious factor in spreading spotted fever in nature, and indirectly in spreading the disease to man.

It is not impossible that ticks unstudied from this aspect, such as the animal (and human) ear tick, *Otiobius megnum*, Duges, 1883, and other species of the Argasidae may some day be found to transmit spotted fever to man.

Whether spotted fever can be transmitted by species of the Clinocoridae (bed bugs) or the Siphonaptera (lice) has never been proven or disproven.

Nymphs of *D. andersoni* have twice been known to infect infants, but usually only adult ticks are known to feed on man. The disease has been transmitted to small rodents by means of larval and nymphal ticks, and these are not uncommon vectors under natural conditions.

American mountain tick-fever is not known to occur outside of the distribution area of *D. andersoni*. In fact it does not occur over the whole of the *D. andersoni* distribution area; the northwestern half of the latter apparently not being concerned with mountain fever. In this connection it is well to note that the common wood-tick of Idaho and Nevada had early in uncertain taxonomic place at one time being confounded with *D. occidentalis* and at another time being set up as a separate species *D. medialis*. These varietal differences within *D. andersoni* apparently occur but whether the western variety *D. andersoni* or *D. medialis* is incapable of transmitting

or less protracted period of convalescence, often of several months, during which it is often impossible for the patient to resume his usual occupation¹⁸⁷

The marked prevalence of spotted fever among sheep herders and others concerned with range management of sheep is frequently a real problem for wool growers, and in some sections is a factor which merits and receives serious consideration^{91,104}

THE VIRUS IN NATURE

Reservoirs Investigations in Montana have shown the following rodents to be susceptible to spotted fever: the Columbian ground squirrel, *Citellus columbianus*, the side striped squirrel, *Callospermophilus leucurus cinerascens*, the woodchuck, *Marmota flaviventris*, the pine squirrel, *Sciurus hutchinsoni*; the white bellied chipmunk *Eutamias q. umbrinus*, the yellow bellied chipmunk, *Eutamias b. luteiventris*, the wood rat, *Neotoma cinerea*, the snowshoe rabbit, *Lepus harrisi*, the cottontail rabbit, *Sylvilagus nuttalli*, the white tailed jack rabbit, *Lepus t. campestris*, the prairie dog, *Cynomys l. ludovicianus* (Ord), the badger, *Taxidea taxus* (Schreber); and the weasel, *Putorius arizonensis*

Character of the Virus The virus of spotted fever has been described as having two phases, a non-virulent phase capable of producing immunity but incapable of producing clinical manifestations of infection, and a virulent phase that causes the clinical manifestations of spotted fever and also a permanent (or a long lasting) immunity. This bi-phasic character of the virus is the probable explanation of

certain features of the disease that were for long inexplicable. However, the biodynamics of this character of the virus have not yet been elucidated. The virus of spotted fever does not pass through a Berkefeld filter.

The virus of *mountain fever* seems not to have any biphasic character. It possibly can be identified with the filter passing virus recovered from the wood-tick (*D. andersoni*) by Noguchi.

Virulence *Mountain fever* does not differ greatly in virulence from year to year or with respect to the locality where acquired. There are minor variations in the clinical course of the disease in different outbreaks and there are two main varieties of clinical type, the relapsing type and the typhoidal type. Several clinicians have, however, remarked upon the great similarity of all cases of American mountain tick-fever as observed in a given epidemic.

Spotted fever is unique in the fact that the virulence varies greatly in different localities but that the virulence of the infection in any locality is reasonably constant. The areas of greatest known virulence are the west side of the Bitter Root Valley in western Montana, a small section on Kirby Creek near Thermopolis, in Hot Springs County, Wyoming, and an area in the Wind River mountains in Fremont County, Wyoming. In these sections the mortality is high, not infrequently reaching 80 to 100 per cent. The area of mildest infection is in the Snake River Valley in southern Idaho where the mortality seldom exceeds five per cent. Areas of intermediate virulence occur in other sections of the Rocky Mountain region. Ambulatory cases

are not uncommon in southern Idaho and eastern Oregon¹⁸⁷

Mechanics of Transmission For both mountain fever and spotted fever the method of transmission is grossly the same, namely a fixation (bite) of a virulent tick in the human skin for the purpose of engorgement. In the instance of both diseases the virus is transmitted not mechanically, or by the feces, but in the suctorial juices inoculated by the tick during the process of engorgement. There are, however, slight time differences between spotted fever and mountain fever. In spotted fever the tick, even though potent with a highly virulent strain of spotted fever, does not become infective under one and three-quarter hours of fixation. The high proportion of non-immunes infected during certain epidemics (from one-fourth to one-half) leads to the inference that so long a time for infectivity to develop is not present in mountain fever.

ACTUAL AND POSSIBLE VECTORS

Spotted fever is known to be transmissible to man by means of the following species of ticks: the western wood tick *Dermacentor andersoni*, Stiles, 1908¹⁷², the California tick *Dermacentor occidentalis*, Marx, in Utah by *Painnapeptus marginatus*, by *Dermacentor albipictus*, Packard, in the northern plains by *Amblyomma americanum* (Linnaeus) and in the eastern-southeastern states by the dog-tick, *Dermacentor variabilis* (Say) Banks, 1908. These ticks also feed on small rodents. No infected *D. albipictus* have been recovered from nature in spite of repeated tests.

Haemaphysalis leporis - palustris, Packard, a rabbit-tick, feeds on all species of rabbits and on game birds but is known not to feed on man. It is, however, a potent and very serious factor in spreading spotted fever in nature, and indirectly in spreading the disease to man.

It is not impossible that ticks unstudied from this aspect, such as the animal (and human) ear tick, *Otiobius megumi*, Duges, 1883, and other species of the Argasidae may some day be found to transmit spotted fever to man.

Whether spotted fever can be transmitted by species of the Cimicoridae (bed bugs) or the Siphonaptera (lice) has never been proven or disproven.

Nymphs of *D. andersoni* have twice been known to infect infants, but usually only adult ticks are known to feed on man. The disease has been transmitted to small rodents by means of larval and nymphal ticks, and these are not uncommon vectors under natural conditions.

American mountain tick-fever is not known to occur outside of the distribution area of *D. andersoni*. In fact it does not occur over the whole of the *D. andersoni* distribution area, the northwestern half of the latter apparently not being concerned with mountain fever. In this connection it is well to note that the common wood-tick of Idaho and Nevada had early an uncertain taxonomic place at one time being confounded with *D. occidentalis* and at another time being set up as a separate species *D. modestus*. Thus, varietal differences within *D. andersoni* apparently occur but whether the western variety *D. andersoni sensu modestus* is capable of transmitting

mountain fever remains to be proved Whether under natural or laboratory conditions the virus of mountain fever can be transmitted to man by an arthropod other than *D andersoni*, remains to be ascertained.

Incidence of Tick Virus in Nature
In endemic areas of *spotted fever*, only about one out of every two hundred ticks caught at random are virulent for spotted fever

What proportion of the ticks in an endemic area of *mountain fever* are able to infect man is not known, but from the rapidity with which some epidemics of mountain fever develop, and the high percentage (twenty-five to fifty per cent) of cases among known non-immune groups, it would appear that most ticks in mountain fever endemic area are able to transmit mountain fever to man.

MORBIDITY STATISTICS

Spotted Fever. The morbidity rate varies for different localities, and in a given locality to some extent from year to year, although the virulency in any

given locality is reasonably constant The following table gives the number of cases reported to the Boards of Health in the States and years indicated

No statistics have been published as to what per cent of the population in an endemic area have an acquired immunity, but in the southern part of Idaho a very large per cent of the sheep herders are known to have recovered from the mild form of spotted fever.

As to *mountain fever* we have no abundance of satisfactory records concerning morbidity, but in certain portions of western Colorado, south-western Wyoming and north-eastern Utah, mountain fever undoubtedly has a very high morbidity rate Major Kieffer wrote of it as though it occurred commonly at Fort D S Russell (south of Cheyenne, Wyoming), but gave no statistics

At Fort Bridger, Wyoming, Capt Charles Smart, U. S A , found that over an eight year period of time a military command with a mean strength averaging 145 men for the six months (March to August), had cases per

TABLE I
Number of Cases by States and Years

	1915	'16	17	'18	'19	'20	'21	'22	'23	'24	'25	26	Total	Annual Avg
Idaho	360	151	154	103	165	170	204	168	(Extended to)				2210	184
Wyoming	61	27	15	4	6	20	3	77	27	34	37	110	421	45
Nevada	8	20	11	1	2	4	9	1	13	0	11	0	86	8
Montana	42	21	21	10	12	25	27	58	48	44	31	32	371	31
Oregon	53	27	22	13	32	36	45	68	32	13	23	20	303	31
Utah	15	31	15	5	10	9	8							
Colorado	14	5	6	1	2	8	2	11	6	6	4	0	65	6
Washington	8	1	2			2	3	5	1	5	1	1	31	3
California	12	11		3	3	3	11	5	3	6	3	3	13	5
South Dakota	3							3	1		2	2	11	
North Dakota					1		1					1	3	
Total	595	290	252*	143*	253	277	313	325						

*The figures for 1917 and 1918 are probably due in part to the abstraction of men from military service during the World War

TABLE 2
Rates per 100,000 of Population (1915-1926)

States with state-wide or nearly state-wide distribution		
Idaho, 42 66	Wyoming, 17 00	Montana, 5 64
States with half or nearly half state-wide distribution		
Nevada,	10 33 or for affected (Northern) portion	21 00
Oregon,	4 05 or for affected (Eastern) portion	8 00
Utah,	3 68 or for affected (Northern) portion	7 50
Colorado,	0 63 or for affected (Western) portion	1 50
Washington,	0 22 or for affected (Eastern) portion	0 50
States with approximately one-tenth state-wide distribution		
California,	0 30 or for affected (North-east) portion	3 00
South Dakota,	0 15 or for affected (Western) portion	1 50

thousand of mountain fever as follows in March, 1 49, in April, 1 62, in May, 5 60, in June, 13 89, in July, 9 47, and in August, 4 26, totaling 36 33 for the tick season, or an incidence of 5 2 cases a year for a command of 145 men. The rate of 3633 per hundred thousand is 85 times the Idaho, or maximum known morbidity rate for spotted fever. Fort Bridger was undoubtedly a heavily infested locality where the men were well exposed and where the varying composition of the command from year to year gave little opportunity for the population to become stable and immune. Errors in diagnosis may have increased the rate somewhat but not enough to raise it 85 times above the state-wide Idaho rate. Indeed,

that only five cases a year were diagnosed as mountain fever is excellent evidence that rheumatism, bronchitis and other common ailments were not called mountain fever just because observed at high altitudes, as has been alleged by some.

In Colorado the reported cases of mountain fever slightly exceed those of spotted fever but the comparison is very misleading as most cases of spotted fever are reported, but undoubtedly a small part only of the cases of mountain fever owing to their being benign and frequently overlooked or incorrectly diagnosed.

MORTALITY STATISTICS

Mountain fever has no known mortality.

TABLE 3
Recent Montana Statistics

Year	No. of Cases	Deaths	Mortality Rate
1922	58		
1923	48		
1924	44		
1925	31	10	33%
1926	32		
1927	35	5	14%
1928	29		
1929	20	7	35%

Annual average (whole state) 1914 to 1928 31 cases per year, average of 9 deaths per year. From 1917 to 1926 there were 369 cases with 89 deaths, or a death rate of 40 34 per cent. Mortality rate for Bitter Root Valley, 1916-1918, children, 50 per cent, adults 84 91 per cent, all cases, 76 81 per cent.

mountain fever remains to be proved. Whether under natural or laboratory conditions the virus of mountain fever can be transmitted to man by an arthropod other than *D andersoni*, remains to be ascertained

Incidence of Tick Virus in Nature
In endemic areas of *spotted fever*, only about one out of every two hundred ticks caught at random are virulent for spotted fever

What proportion of the ticks in an endemic area of *mountain fever* are able to infect man is not known, but from the rapidity with which some epidemics of mountain fever develop, and the high percentage (twenty-five to fifty per cent) of cases among known non-immune groups, it would appear that most ticks in mountain fever endemic area are able to transmit mountain fever to man

MORBIDITY STATISTICS

Spotted Fever The morbidity rate varies for different localities, and in a given locality to some extent from year to year, although the virulency in any

given locality is reasonably constant The following table gives the number of cases reported to the Boards of Health in the States and years indicated

No statistics have been published as to what per cent of the population in an endemic area have an acquired immunity, but in the southern part of Idaho a very large per cent of the sheep herders are known to have recovered from the mild form of spotted fever

As to *mountain fever* we have no abundance of satisfactory records concerning morbidity, but in certain portions of western Colorado, south-western Wyoming and north-eastern Utah, mountain fever undoubtedly has a very high morbidity rate Major Kieffer wrote of it as though it occurred commonly at Fort D S Russell (south of Cheyenne, Wyoming), but gave no statistics

At Fort Bridger, Wyoming, Capt Charles Smart, U S A., found that over an eight year period of time a military command with a mean strength averaging 145 men for the six months (March to August), had cases per

TABLE I
Number of Cases by States and Years

	1915	'16	'17	'18	'19	'20	'21	'22	'23	'24	'25	26	Total	Annual Avg
Idaho	360	151	154	103	165	170	204	168	(Extended to)				2210	181
Wyoming	61	27	15	4	6	20	3	77	27	34	37	110	421	35
Nevada	8	20	14	4	2	4	9	1	13	0	11	0	86	8
Montana	42	21	21	10	12	25	27	58	48	44	31	32	371	31
Oregon	53	27	22	13	32	36	45	68	32	13	23	29	393	33
Utah	35	34	15	5	10	9	8							
Colorado	14	5	6	1	2	8	2	11	6	6	4	0	65	6
Washington	8	3	5			2	3	5	1	5	1	1	34	3
California	12	11		3	3	3	11	5	3	6	3	3	63	5
South Dakota	3							3	1			2	11	
North Dakota					1		1					1	3	
Total	596	299	252*	143*	233	277	313	395						

*This recession was probably due in part to the abstraction of men from infested areas by reason of military service during the World War

TABLE 2
Rates per 100,000 of Population (1915-1926)

States with state-wide or nearly state-wide distribution		
Idaho, 42 66	Wyoming, 17 00	Montana, 5 64
States with half or nearly half state-wide distribution		
Nevada,	10 33 or for affected (Northern) portion	21 00
Oregon,	4 05 or for affected (Eastern) portion	8 00
Utah,	3 68 or for affected (Northern) portion	7 50
Colorado,	0 63 or for affected (Western) portion	1 50
Washington,	0 22 or for affected (Eastern) portion	0 50
States with approximately one-tenth state-wide distribution		
California,	0 30 or for affected (North-east) portion	3 00
South Dakota,	0 15 or for affected (Western) portion	1 50

thousand of mountain fever as follows in March, 1 49, in April, 1 62, in May, 5 60, in June, 13 89, in July, 9 47, and in August, 4 26, totaling 36 33 for the tick season, or an incidence of 5 2 cases a year for a command of 145 men. The rate of 3633 per hundred thousand is 85 times the Idaho, or maximum known morbidity rate for spotted fever. Fort Bridger was undoubtedly a heavily infested locality where the men were well exposed and where the varying composition of the command from year to year gave little opportunity for the population to become stable and immune. Errors in diagnosis may have increased the rate somewhat but not enough to raise it 85 times above the state-wide Idaho rate. Indeed,

that only five cases a year were diagnosed as mountain fever is excellent evidence that rheumatism, bronchitis and other common ailments were not called mountain fever just because observed at high altitudes, as has been alleged by some.

In Colorado the reported cases of mountain fever slightly exceed those of spotted fever but the comparison is very misleading as most cases of spotted fever are reported, but undoubtedly a small part only of the cases of mountain fever owing to their being benign and frequently overlooked or incorrectly diagnosed.

MORTALITY STATISTICS

Mountain fever has no known mortality.

TABLE 3
Recent Montana Statistics

Year	No of Cases	Deaths	Mortality Rate
1922	58		
1923	48		
1924	44		
1925	31	10	33%
1926	32		
1927	35	5	14%
1928	29		
1929	20	7	35%

Annual average (whole state) 1914 to 1928 31 cases per year, average of 9 deaths per year. From 1917 to 1926 there were 369 cases with 89 deaths, or a death rate of 24 34 per cent. Mortality rate for Bitter Root Valley, 1916-1918, children, 50 per cent; adults 84 91 per cent, all cases, 76 81 per cent.

Spotted fever prior to 1910, statistics were available only for Idaho and Montana. The best available statistics gave for Idaho a rate fluctuating from year to year between 4 per cent and 7 per cent (Maxey's average, 4.86 per cent) and for Montana (Bitter Root Valley) from 40 per cent to 70 per cent with occasional annual extremes of 35 per cent to 100 per cent.

Next to Montana in order of mortality Wyoming (1922-1926) 22.80 per cent, Colorado (1913-1926) 18.18 per cent, Oregon (1913-1926) 17.28 per cent, Nevada (1911-1926) 11.81 per cent, Washington (1912-1926) 11.11 per cent, California (1903-1926) 10.53 per cent, Idaho 4.86 per cent. Average (uncorrected) 19 per cent, corrected by weighting, 12.4 per cent. Mortality rate among American Indians (as reported by Dr. Welty) Arapahoes, 20 per cent, Shoshones, 16.6 per cent.

The annual loss of life from spotted fever in the western endemic area now closely approximates one-eighth (12.5 per cent) of 600 cases a year, or between 70 and 80 deaths annually. With the addition of the deaths from spotted fever in the eastern-southeastern states endemic area the total for the whole country is about 100 to 110 deaths annually.

The mildest infection is in the Snake River Valley in Idaho where the mortality seldom exceeds 5 per cent.

Within the eastern-southeastern states endemic area at least 93 cases were known to occur in five states and the District of Columbia in the Spring and Summer of 1930 with 21 deaths—a case fatality rate of 22.6 per cent. In the Rumranch-Dyer-Badger selected

series of 50 cases, there was death of seven patients or 14 per cent.

The areas of greatest virulence are on the west side of the Bitter Root Valley in western Montana, a small section of Kirby Creek near Thermopolis in Hot Springs County, Wyoming, and an area in the Wind River mountains in Fremont County, Wyoming. The mortality in these sections not infrequently reaches from 80 per cent to 100 per cent. In southern Idaho near Soda Springs, an area of 100 per cent mortality was formerly known, but no cases have been reported since 1903. A group of very virulent cases was reported from Boise, Idaho, in 1929.

Of five consecutive cases occurring as laboratory infections among unvaccinated laboratory workers, all died.

SUMMARY

The epidemiography of two tick-borne diseases, each clinically distinguishable from the other, is found not to be conformable in all respects.

The mountain or more benign fever has been reported only from an area within the range of distribution of spotted fever, but it has not been observed over the whole of the spotted fever area of the Rocky Mountain region, nor is it known to occur in the eastern-southeastern states area of spotted fever.

Mountain fever is apparently limited by barriers peculiar to itself as it has not recently spread, or been carried, into new localities as has spotted fever. In fact, while the distribution area of spotted fever is slowly spreading, that of mountain fever is apparently less than it was formerly.

American mountain tick-fever is predominantly acquired within the upper timber reaches of the mountain valleys, and for the most part at a distinctly higher altitude than spotted fever, which is a disease of the valleys and inter-mountain plateaus whereas mountain fever is most prevalent in the timbered regions and high mountain passes

A longer seasonal incidence is observed for mountain fever than for spotted fever

Mountain fever has, in ratio to population, a very much greater prevalence than the largest morbidity rate known for spotted fever, which fact may indicate either a greater tick infestation ratio or that the virus of

mountain fever is not subject to a phase of latency as is that of spotted fever

Spotted fever is a seriously incapacitating disease with an average mortality of 12.4 per cent, and great economic importance, whereas mountain fever is a benign disease of no known mortality and trifling economic importance

Neither the virus nor the natural reservoirs of mountain fever are known but from data at hand it seems reasonable to suspect that rabbits, spermophiles, prairie dogs and chipmunks are immune to the disease, and that the reservoir should be looked for in mountain rats, badgers, and probably squirrels

REFERENCES

- ¹COBB, J. O. The so-called "spotted fever" of the Rocky Mountains—a new disease in Bitter Root Valley, Pub Health Rep, U S Pub Health and Mar Hosp Serv, 1902, xvii, 1868-1870
- ¹³GATES, G. A. A report of two cases of "spotted fever", 2d Bien Rep Montana St Bd Health (1902-1904), 1905, pp 158-160
- ¹⁹ANDERSON, J. F. Spotted fever (tick fever) of the Rocky Mountains. A new disease, 2d Bien Rep Montana St Bd Health (1902-1904), 1905, pp 123-158
- ²⁶BRADEN, J. M. Some observations on four cases of spotted fever occurring in Colorado, Colorado Med, 1906, iii, 213-219
- ²⁸MOOSER, CHARLES E. Rocky Mountain spotted fever, Jr Am Med Assoc, 1906, xlvii, 686
- ³²COOLEY, R. A. Control of the Rocky Mountain spotted fever tick in Montana, 4th Bien Rep Montana St Bd Health, 1908, p 137
- ⁵⁰STATES, G. W. Tick Fever or Rocky Mountain spotted fever, Utah Med Jr (Denver Med Times), 1909, xlviii, 522-526, discussion, 568-571
- ⁷⁴BISHOPP, F. C. The distribution of the Rocky Mountain spotted fever tick, Circular No 136, Bur Entomol, U S Dept Agric, 1911, 1-4
- ⁷⁸RUCKER, W. C. Rocky Mountain spotted fever, Reprint from Pub Health Rpts No 96, Wash, D C, Govt Print O, 1912. Supersedes Pub Health Rpts, xxvii, 1465-1482, and Military Surgeon, 1911, xxix, 631-657
- ⁸⁷BISHOPP, F. C., and KING, W. V. Additional notes on the biology of the Rocky Mountain spotted fever tick. Jr Leon Ent, 1913, vi, 200-211
- ⁹¹COOLEY, R. A. Report as secretary of the Montana State Board of Entomology, 1st Bien Rpt Montana St Bd of Entom, 1915, pp 5-12
- ¹⁰¹COOLEY, R. A. Report as secretary of the Montana State Board of Entomology, 2d Bien Rpt Montana St Bd of Entom, 1917, pp 5-12
- ¹¹²COOLEY, R. A. Report as secretary of the Montana State Board of Entomology, 3d Bien Rpt Montana St Bd of Entom, 1919, pp 5-23

- ¹¹⁵PARKER, R R . Second Report on Investigations of the Rocky Mountain spotted fever tick in eastern Montana, 3d Bien Rpt Montana St Bd of Entom, 1919, pp 41-54
- ¹²¹WOLBACH, S BURT Rocky Mountain spotted fever, Nelson's Loose Leaf Medicine, 1920, II, 215-217F, and The Oxford Medicine, 1921, v 467-484
- ¹²⁴PIERCE, WILLIAM DWIGHT Sanitary Entomology, 1921, Richard G Badger, Boston
- ¹³⁵TONKIN, A B Incidence of Rocky Mountain spotted fever in Wyoming, Special Bull No 26, Montana St Bd Health, 1923, pp 23-27
- ¹³⁶SIMPSON, A U Rocky Mountain spotted fever in the State of Washington, Special Bull No 26, Montana St Bd Health, 1923, pp 20-23
- ¹⁵²INTERNATIONAL COMMISSION ON ZOOLOGICAL NOMENCLATURE Opinion No 78, Smithsonian Miscel Coll, 1924, lxxiii, 1-14
- ¹⁶⁷FRICKS, LUNSFORD D Rocky Mountain spotted fever, Tice's Practice of Medicine, 1926, v 49-67
- ¹⁷⁸GYDESEN, C S Rocky Mountain spotted fever and case report, Colorado Med, 1928, xxv, 46-51
- ¹⁸⁰PERRY, J C Rocky Mountain spotted fever as bearing on public health in western states, California and West Med, 1928, xxix, 217-221
- ¹⁸⁷PARKER, R R Rocky Mountain spotted fever, 7th Bien Rep Montana St Bd of Entom, 1928, pp 39-62
- ¹⁹¹LEVIN, W Certain public health problems of Oregon, Jr Kansas Med Soc, 1929, xxx, 345-347
- ¹⁹³KERLEE, A L, and SPENCER, R R Rocky Mountain spotted fever A preliminary report on the Weil-Felix reaction, U S Pub Health Rep, 1929, xlv, 179-182
- ¹⁹⁵SPENCER, R R Rocky Mountain spotted fever, Billings-Forchheimer therapeutics of internal disease, Supplement to Blumer Ed 1929, D Appleton, New York, pp 289-296
- ²¹⁵PIERCE, C M, and VANDERKAMP, H Rocky Mountain spotted fever in Nebraska,, Nebraska Med Jr, 1931, vi, 69-71

Thrombo-Angiitis Obliterans Among Persons Past Middle Age*†

By BAYARD T. HORTON, M.D., F.A.C.P., and GEORGE E. BROWN, M.D.,
F.A.C.P., Rochester, Minn.

THROMBO-ANGIITIS obliterans usually occurs among men between the ages of twenty-five and fifty years. In a recent study of 150 proved cases by Brown and Allen the youngest patient was aged seventeen years and the oldest sixty-four, only two in the series were more than sixty years. Four other patients have since been observed at the clinic: a woman aged sixty years², a man aged sixty-three years with involvement of the left hand and both lower extremities, a man, aged sixty-five years, who gave a typical history of intermittent claudication in the arches and muscles of the calf for a period of thirty years, and a man, aged seventy-three years, the oldest patient with this disease observed at The Mayo Clinic, and, so far as we know, the oldest proved case on record.

With early diagnosis, improved methods of treatment, and the prophylactic measures which are being carried out in these cases, it is highly probable that a larger percentage of patients will reach the later decades of life without amputation. It is common to find arteriosclerosis of the extremities

of patients aged from fifty to sixty years, combined lesions of thrombo-angiitis obliterans and arteriosclerosis are also commonly found in this age group, and either lesion may predominate in a given case. Patients with thrombo-angiitis obliterans in the sixth and seventh decades of life represent a very small percentage of the total number with this disease, as is evidenced by the fact that only six patients aged more than sixty years were observed in a series of more than 500.

REPORT OF CASES

Case 1 A man, aged sixty-three years, registered at The Mayo Clinic June 4, 1926. His chief complaint was pain in the left foot. His health had always been good. He had been an excessive user of tobacco for many years. Five years prior to admission small painful, raised reddish and bluish lumps along both legs developed. With rest, the condition cleared in two or three months. Two years later pain, tenderness and swelling of both legs developed. This had disappeared, by rest and elevation of the extremities, at the end of two weeks. In September, 1923, an ulcer appeared on the fifth right toe. It failed to heal and caused excruciating pain. The toe was amputated in February, 1924. The wound healed promptly and the patient went back to work feeling perfectly well and remained well until May or June, 1925. At this time a sore spot appeared on the distal plantar surface of the left foot, associated with intermittent pain

*Submitted for publication April 3, 1931.

†From the Division of Medicine, The Mayo Clinic, Rochester, Minnesota.

He continued to work most of the time until October 1, 1925, when a painful ulcer developed between the fourth and fifth toes, which did not heal. All of the toes on the left foot were amputated October 30. There was incomplete healing, and two discharging sinuses were still present at the time of admission to the clinic. Considerable pain was present. He had had intermittent claudication pain in the arch of the right foot for eight months. He had had weakness in the left hand for three months, when he attempted to work. Paresthesia was not observed.

The general examination was essentially negative, except for the condition of the extremities. The systolic blood pressure was 136 and the diastolic, 90, in millimeters of mercury. The right radial and ulnar arteries pulsated normally, but pulsations could not be felt in the left radial and ulnar arteries.

Definite postural color changes in the hands were not observed. Small pulsations could be felt in both femoral arteries, but pulsations were absent in both popliteal, both dorsalis pedis and both posterior tibial arteries. There were two small draining sinuses in the stump of the left foot. With the feet elevated, there was pallor, graded 1 to 2 of the right foot and graded 3 to 4 of the left foot. When the feet were lowered to the dependent position, there was rubor, graded 3, of the toes of the right foot in thirty seconds, and rubor, graded 4, of the left foot in three minutes. This indicated a slow return of blood to the left foot. Both feet felt cold. There was atrophy, graded 1, of the left thigh and leg. The neurologic examination showed a decrease in sensation of touch, pain and temperature, graded 2 to 3. The other neurologic data indicated arteriosclerosis of the central nervous system. Examination of the

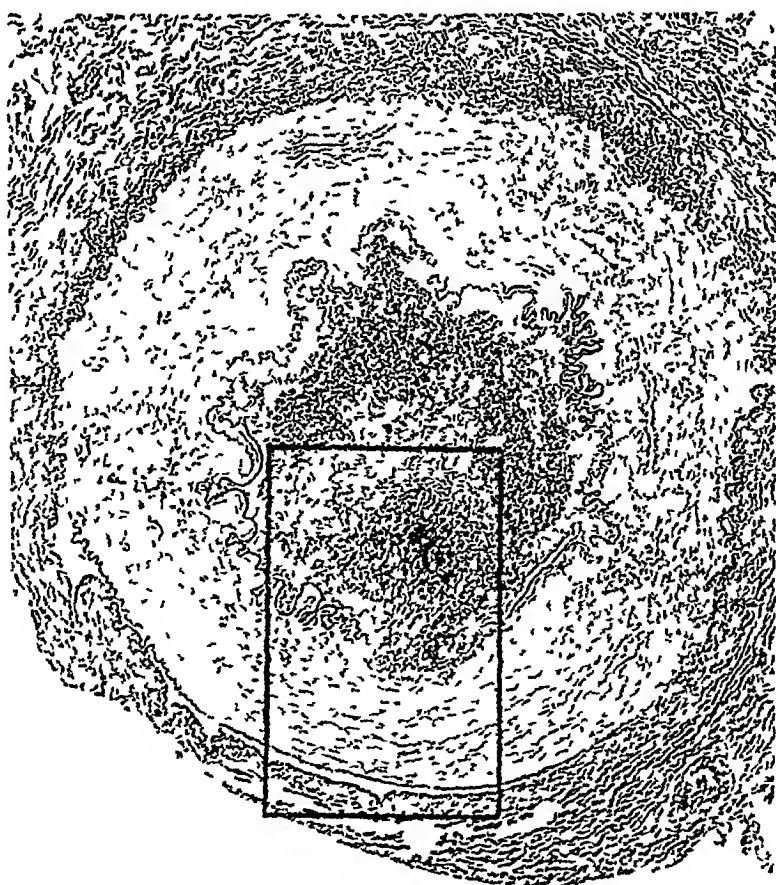


FIG. 1. Cross section of the posterior tibial artery at the level of the ankle. The lumen is occluded by a recent partially organized cellular thrombus, in which lymphocytes and endothelial leukocytes are the predominating cells. A few polymorphonuclear leukocytes are present. Calcification of the wall of the vessel is not present (hematoxylin and eosin stain, $\times 35$).

urine and the Wassermann reaction of the blood were negative. The hemoglobin (Dare) was 70 per cent, erythrocytes numbered 4,310,000, and leukocytes 9,700 in each cubic millimeter of blood. The concentration of urea was 34 mg for each 100 c.c. of blood, and the creatinine 11 mg. The glucose tolerance test was negative. The return of phenolsulphonphthalein was 45 per cent in two hours. Roentgenograms of the legs were negative for calcified vessels.

One intravenous injection of triple typhoid vaccine was given, with a rise in systemic temperature of 36°F , but there was no rise in the surface temperature of the feet. Because of the patient's age, the severity of the pain, the prolonged healing with draining sinuses, and the absence of a rise in surface temperature in the left foot following the typhoid vaccine, amputation of the left leg was advised, but was refused. The patient went home eight days after admission.

Four months later the patient's home physician stated that the two sinuses had closed approximately half, he felt that amputation of the left leg was advisable. In July, 1927, the patient wrote that one sinus had entirely closed and that the other one had practically closed. He was free from pain and had gained 215 pounds in weight. He stated that a good pulse could be felt in front of the left ankle. In July, 1929, he again wrote that his general health was excellent and that the left foot had entirely healed. The foot still felt tender, but he was able to walk with the aid of a crutch.

A diagnosis of thrombo-angitis obliterans was made in this case because of the long history, the observations at general examination, especially the involvement of the left arm with occlusion of the left radial and ulnar

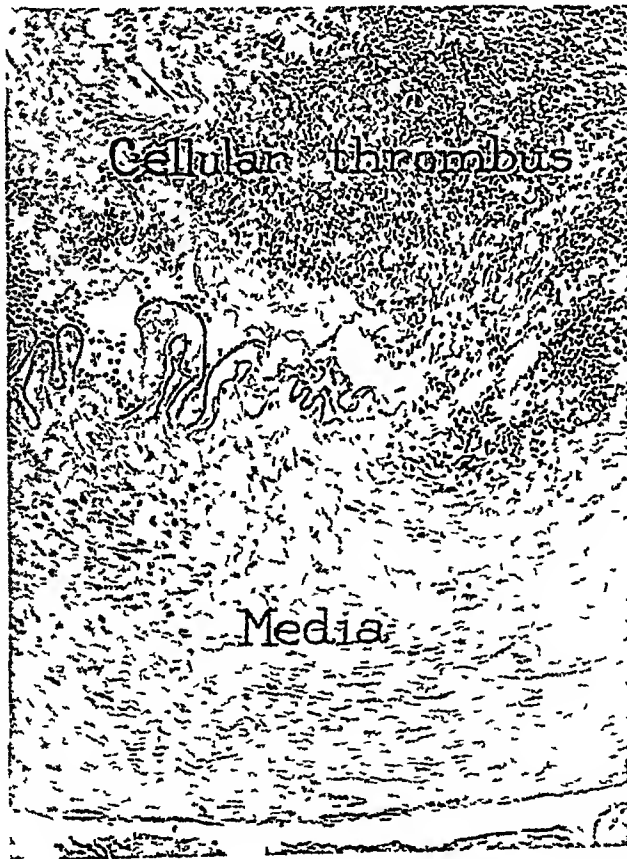


FIG 2 A higher power of figure 1 showing more cellular detail and representing the rectangular area in figure 1 (hematoxylin and eosin stain $\times 150$)

arteries, the history of chronic, relapsing superficial phlebitis, and the later course of the disease. Occlusion of vessels of the hand is common in cases of thrombo-angitis obliterans but is extremely rare in arteriosclerosis. Many patients with thrombo-angitis obliterans with ulcers and trophic lesions could probably avoid amputation of the involved extremity, if they were willing to endure pain as this patient did. In many of our cases amputation is done because of pain rather than because of the extent of the gangrene or of the trophic changes.

Case 2 A man, aged sixty-five years, registered at The Mayo Clinic October 23, 1929. He complained chiefly of intermittent pain in the legs, and hemoptysis. He had smoked an average of seven small cigars daily since the age of twenty. For the last thirty years he had had arch fatigue and pain of the intermittent claudication type, and had worn many arch supports without relief. For the last fifteen years he had had mild intermittent claudication in the calves. At the time of admission he could walk only two city blocks without this pain. Rest for a few minutes always gave prompt relief. During the last year he had complained of cold feet, and observed that they were blushed when in the dependent position. For the last four months he had intermittent rest pain in the first and second left toes. Seven

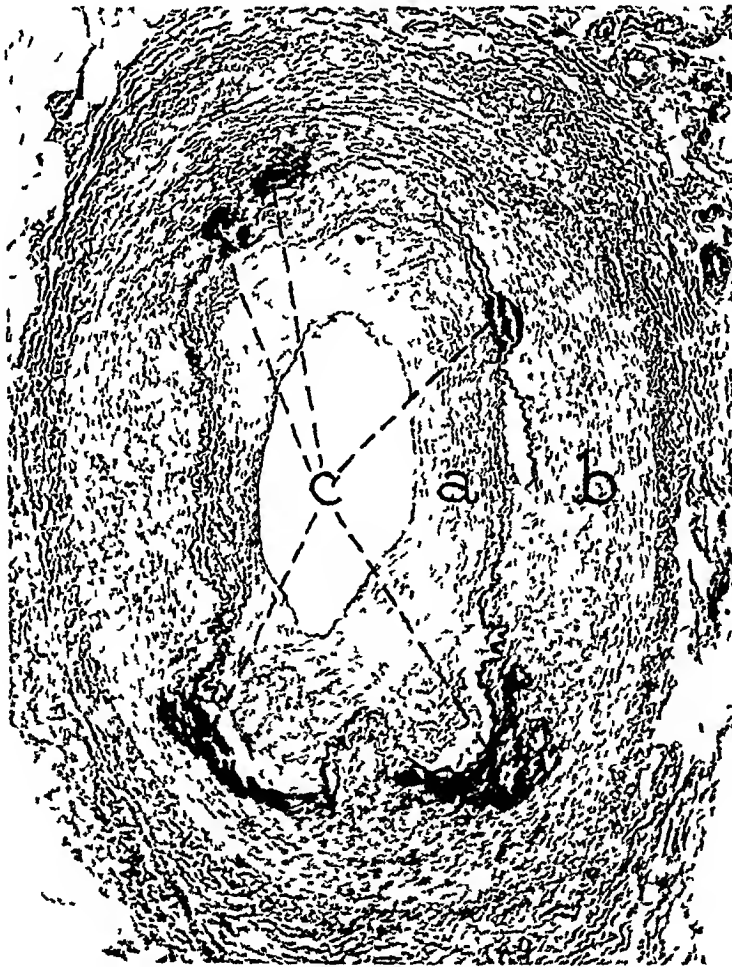


FIG. 3 Cross section of the posterior tibial artery from a subject with arteriosclerosis. Deposits of calcium salts (c) are present in the media (b). The intima (a) is thickened and is comparatively acellular (hematoxylin and eosin stain x35).

months prior to admission productive cough frequently with blood-tinged sputum developed following a "cold" On a few occasions he had coughed up 30 c.c. or more of bright red blood There was no definite history of superficial phlebitis

The patient appeared to be moderately well nourished, was approximately 5½ feet in height, and weighed 130 pounds The thorax was barrel-shaped, with definite limitation in expansion Râles were not present either before or after expiratory cough Roentgenograms of the thorax showed ancient healed tuberculosis at the right apex Examination of the sputum was negative for the bacillus of tuberculosis The possibility of hemoptysis from a small area of bronchiectasis was considered The heart showed compensatory cardiac hypertrophy, graded 1

The systolic blood pressure on admission was 175 and the diastolic 90, in millimeters of mercury While the patient was under observation in the hospital the systolic pressure was 130 and the diastolic 60 All of the palpable vessels in the upper extremities pulsated normally Both femoral arteries pulsated normally, and slight pulsation could be felt in the right popliteal artery, but pulsations could not be felt in the left popliteal artery or in the arteries of the feet The arches in both feet appeared normal With elevation of the feet, there was moderate blanching of the toes of the left foot With the feet in the dependent position there was rubor, graded 1, of the toes of the right foot, graded 2, of the left foot, and moderate cyanosis of the second left toe Examinations of the urine were negative The con-

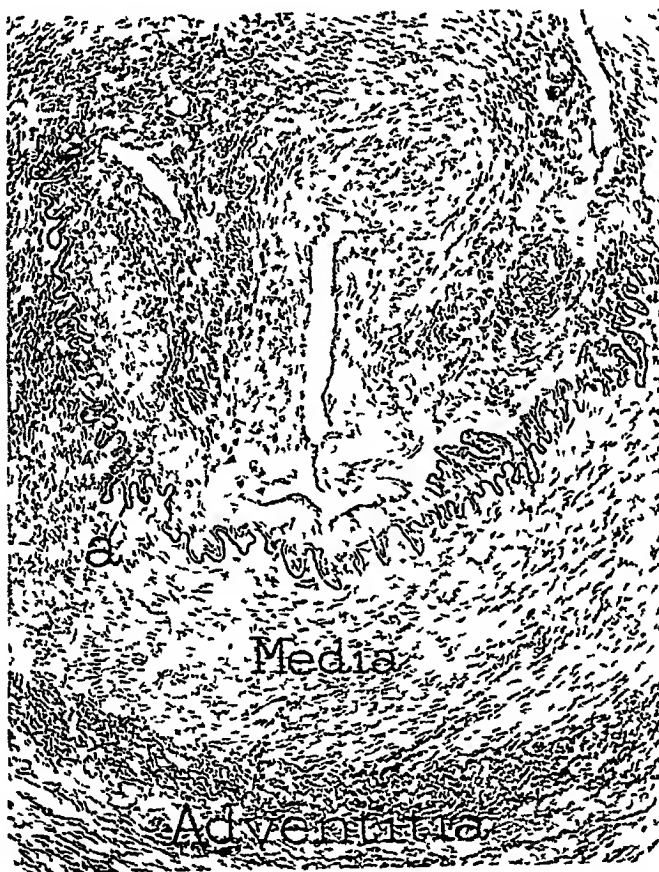


FIG 4 Cross section of the dorsalis pedis artery The lumen is occluded by a partially organized thrombus which has been partially canalized There is absence of calcification in the wall of the vessel The internal elastic membrane (a) appears normal (hematoxylin and eosin stain x80)

centration of hemoglobin was 17.6 gm in 100 c.c., and the leukocytes numbered 9,100 per cubic millimeter. The concentration of blood urea was 34 mg in 100 c.c., and the blood sugar was 90 and 78 mg. The electrocardiogram was essentially negative. The return of phenolsulphonphthalein was 50 per cent in two hours. Roentgenograms of the feet and legs were negative for calcified vessels and for lesions of bone.

Radiant heat was applied to the legs for five to eight hours a day, and postural exercises were carried out three times daily. Intramuscular injections of typhoid vaccine were also given. The patient was instructed to restrict physical activity to the point of not producing pain in the lower extremities. Because of the thirty-year history of intermittent claudication (arterial closure), the slow onset of the disease, and the favorable

response to treatment, we believed that the prognosis was fairly good for preservation of the extremities. However, a letter from the patient dated March 24, 1931, stated that during the past six months the left leg had been amputated (apparently below the knee). The stump did not heal and a second amputation above the knee was necessary.

The long history of occlusive vascular disease beginning at the age of thirty-five years, and the absence in the roentgenogram of evidence of calcification of the vessels make the diagnosis of thrombo-angitis obliterans reasonably certain. The early use of arch supports is also suggestive. This history is the longest of this disease which is on record at The Mayo Clinic.



FIG. 5. Cross section of a deep vein of the left leg. The lumen is occluded by an ancient thrombus which has been canalized (Weigert's elastic tissue stain $\times 40$).

Case 3 A man, aged seventy-three years, was under observation at The Mayo Clinic in April, 1907, November, 1915, and March, 1929. Symptoms referable to the hands and feet were first observed in 1903. These consisted of the three-phase color reaction, white, red and blue, when the hands were exposed to cold. In 1906 the fifth right toe was amputated elsewhere for an unhealed ulcer. At the time of his first admission in 1907 he had an unhealed ulcer on the right great toe. The toe was amputated. During the next five or six years two or three similar ulcers developed which required from six to eight months to heal. At admission in 1915, there were ulcers on the second right and the first and fifth left toes, which had been present for approximately ten months.

Both feet appeared hyperemic in the dependent position. The general examination was otherwise essentially negative. The systolic blood pressure was 126 and the

diastolic 86. Examinations of the urine were entirely negative. The concentration of hemoglobin was 89 per cent and the leukocytes numbered 10,800. The Wassermann reaction of the blood was negative. A roentgenogram of the thorax was negative, except for slight enlargement of the heart, graded 1. Roentgenograms of the feet were negative. It was believed at this time that the ulcers were due to obliterative arterial disease, but record was not made regarding pulsations in the arteries of the feet. However, rest, with the feet in a horizontal position, was advised until adequate collateral circulation was established.

During 1918 and 1919 the second right and the third left toes were amputated elsewhere for unhealed ulcers. It required from two to twelve months for these amputation wounds to heal. During the course of the patient's illness, he had approximately twelve ulcers on the tips of the toes. Fourteen

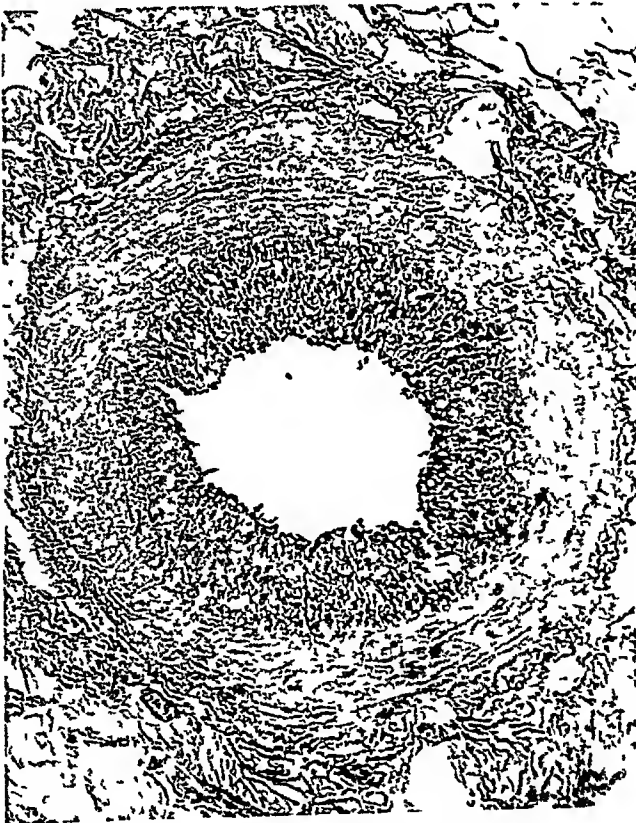


FIG 6 Cross section of a small artery. Cellular thickening of the intima is shown (hematoxylin and eosin stain $\times 135$).

months prior to his third admission, March 6, 1929, an ulcer developed at the base of the left great toe, which gradually increased to about 2 cm in diameter. There was little pain associated with these ulcers. For a period of twenty years, he had noticed an occasional small nodule beneath the skin. Whether these represented areas of superficial phlebitis could not be determined from the history. There was no definite history of intermittent claudication, although for a period of more than twenty years he did very little walking, and always took the best of care of his feet and legs. He had smoked an average of three cigars daily for the last fifty years, and had taken about three drinks of whiskey daily for approximately the same period.

Examination was essentially negative, except for the condition of the extremities. The patient seemed well preserved for his age.

He was about 6 feet 2 inches in height, and weighed approximately 150 pounds. The systolic blood pressure was 120 and the diastolic 76. Both radial arteries pulsated normally but pulsations could not be felt in the ulnar arteries. Both femoral arteries pulsated normally. The pulsations in the right popliteal artery were reduced 50 per cent and pulsation could not be felt in the right dorsalis pedis or posterior tibial arteries. Pulsations could not be felt in the left popliteal, left dorsalis pedis and left posterior tibial arteries. The sclerosis in the peripheral arteries was graded 1. Examination of the urine was negative, except for a slight trace of albumin. The hemoglobin was 12.9 gm in each 100 cc by the acid-hematin method. The erythrocytes numbered 4,380,000 and the leukocytes, 9,300. The differential count showed lymphocytes 13, large mononuclear cells 2, transitional cells 7, and



FIG. 7. Cross section of a small arteriole. Marked cellular thickening of the intima is shown, which almost completely occludes the lumen (hematoxylin and eosin stain $\times 200$).

neutrophils 78 per cent The concentration of urea was 35 mg in 100 c c of blood, uric acid was 276 mg and sugar was 76 mg Roentgenograms of the feet and legs were negative The return of phenolsulphon-phthalein was 40 per cent in two hours The electrocardiographic report showed a rate of

86, auricular premature contractions, and aberrant QRS complex in derivations I and II, notched left ventricular preponderance, notched P wave in derivations I and II and inverted T wave in derivation III

The ulcer at the base of the left great toe gradually increased in size and on the fourth

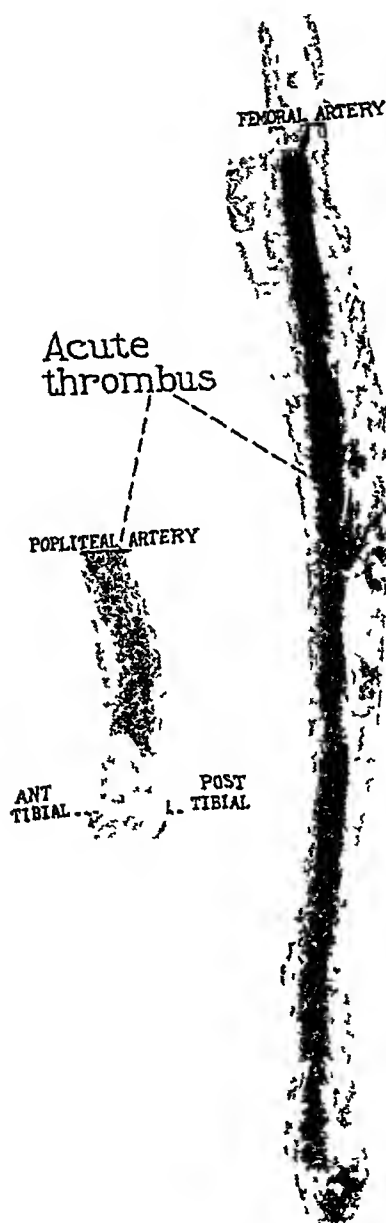


FIG 8 Longitudinal sections of the left femoral and popliteal arteries showing the vessels occluded with an acute thrombus

day after admission the dorsum of the foot became gangrenous. There was also a distinct change in the patient's general condition. The left leg was amputated March 11, 1930, at the juncture of the upper and middle third of the femur. The femoral artery was thrombosed at the site of the amputation. The afternoon of the operation, abdominal distention developed, which could not be relieved either by gastric or colonic lavage. The distention and toxemia increased, the blood urea rose to 130 mg in 100 c.c. the following day, the patient's strength gradually failed, and he died forty-eight hours later, in spite of supportive measures.

At the bifurcation of the popliteal artery of the amputated leg, the vessel was occluded by an ancient and completely organized thrombus, about 1 cm in length. The remainder of the popliteal artery was occluded by a recent red, partially organized

thrombus. The posterior tibial artery was patent to the lower third of the leg. Below this level it was occluded by a partially organized thrombus (figures 1 and 2). Figures 1 and 2 should be compared with figure 3 which is the cross section of the posterior tibial artery of a subject with arteriosclerosis. The anterior tibial and dorsalis pedis arteries were occluded (figure 4) with an ancient organized thrombus. The deep veins were also involved in a similar occlusive process (figure 5). Many of the smaller arteries and arterioles showed active proliferation of intima (figures 6 and 7). At necropsy the left stump did not show evidence of infection, but the skin adjacent to the wound was dark red, indicating a poor blood supply. The left femoral artery (figure 8) was occluded with a recent red thrombus which extended up to Poupart's ligament. The iliac arteries were patent and did not show gross

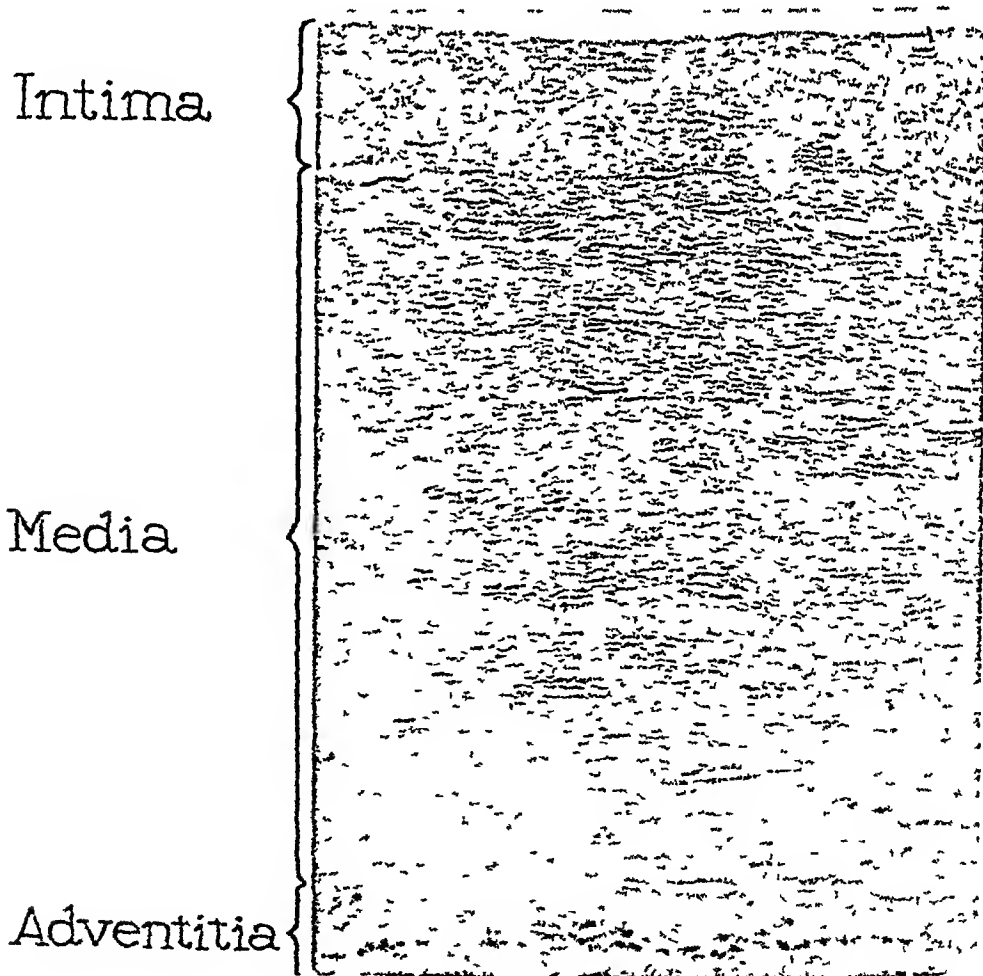


FIG. 9. Cross section of the left external iliac artery. Thickening of the intima is shown (hematoxylin and eosin stain $\times 150$).

evidence of arteriosclerosis but it was shown to be present on microscopic examination (figure 9). The aorta was also patent and showed arteriosclerosis, graded 3 in the arch and upper thoracic portion, and graded 1 to 2 in the abdominal portion. In the abdominal aorta there was an area 3 by 3 cm which was covered with relatively soft necrotic material, it is possible that an embolus may have broken off and lodged in the left popliteal artery, serving as the basis for the propagating thrombus which had completely filled the left popliteal and left femoral arteries. Other significant observations were not made at post mortem examination, except the presence of chronic mitral endocarditis, chronic duodenal ulcer, and mild atrophy of the brain with arteriosclerosis, graded 3, of the arteries composing the circle of Willis. Peritonitis was not present. The heart weighed 429 gm and the coronary arteries showed arteriosclerotic changes, graded 2. The lungs showed evidence of congestion, but pneumonia was not present, either on gross or microscopic examination.

The long history (1903 to 1929) of symptoms in both hands and both feet, the occlusion of both ulnar arteries, the amputation of four toes at irregular intervals and the prolonged healing following, the absence of demonstrable calcification in the vessels by roentgen ray, and the appearance of the microscopic sections from the amputated leg, make the diagnosis of thrombo-angitis obliterans certain. The arteriosclerosis in this case was not more advanced than would be expected among men of that age, in fact, it was not as advanced as we have often noted in younger persons who were having few, if any, symptoms referable to the extremities. The extent of the acute thrombosis in the left femoral artery (the thrombus extended from the bifurcation of the popliteal to Poupert's ligament) makes it doubtful whether the stump would have healed owing to

the marked and sudden diminution in the blood supply to the extremity.

This case calls attention to the fact that age, of itself, does not eliminate thrombo-angitis obliterans. The pathologic changes in the vessels of the amputated leg indicated the presence of chronic inflammatory rather than a degenerative type of disease and proved the diagnosis of thrombo-angitis obliterans. No doubt an erroneous diagnosis of Raynaud's disease was made at the onset of symptoms, because of the color changes in the hands on exposure to cold. It should be emphasized again that the three-phase color reaction in men, when the hands and feet are exposed to cold, does not necessarily indicate Raynaud's disease, it usually indicates an early symptom of thrombo-angitis obliterans. For a period of years, there had been a succession of digital ulcers, and gangrene, with amputation and slow healing. At the patient's subsequent visits to the clinic in 1907 and 1915, the correct diagnosis was not made.

COMMENT

Three cases of thrombo-angitis obliterans in persons aged sixty-three, sixty-five and seventy-three years, respectively, are reported. One patient gave clinical evidence of having had the disease for more than twenty-six years, and another for more than thirty years.

A pathologically proved diagnosis was obtained in one case. One patient, a man aged seventy-three years, is the oldest subject we have seen with this disease, and so far as we are aware is the oldest on record.

The data concerning these patients give additional light on prognosis. The disease is characterized by a chronic relapsing lesion of the vessels, and occlusion and collateral circulation struggle for supremacy. The element of time is most important in this struggle, since on this, preservation of the part rests. If the intervals between relapses are short, and the time for adequate collateral circulation is brief, trophic changes and gangrene are likely to ensue. Conversely, if the intervals of time between relapses are long, collateral circulation becomes adequate and sufficient supply of blood to the distal areas is assured. The first consideration regarding prognosis is the frequency of the exacerbation of the disease. Our experience in a large

number of cases of thrombo-angitis obliterans shows clearly that a high percentage of bad prognoses (regarding amputation) is not justified in this disease. Probably 20 to 30 per cent of patients will lose one or more limbs. An increasing number of early diagnoses, the institution of protective and therapeutic measures, and the institution of protective types of operation, as sympathetic ganglionectomy in selected cases, are still further reducing this percentage. Increasing knowledge by the profession of the dangers of surgical tinkering with the affected digits in which the supply of blood is already diminished will perhaps accomplish greater changes in the prognosis than any other single factor.

REFERENCES

¹BROWN, G. E., and ALLEN, E. V. *Thrombo-angitis obliterans*. Philadelphia, 1928, W. B. Saunders Co., 219 pp.

²HORTON, B. T., and BROWN, G. E. *Thrombo-angitis obliterans in women* (In press).

Treatment of Angina Pectoris With a Tissue Vasodilator Extract—Preliminary Report*†

By JOSEPH B WOLFFE, M D, DONALD FINDLAY, Ph D, and
EDWARD DESSEN, M D, *Philadelphia, Pa*

IN 1926 E K Frey and H Kraut¹ found a substance in the urine which they demonstrated to have vasodilator properties, and which they believed to be a circulation hormone (Kreislaufhormon). In 1929 Frey² operated on a patient who had a pancreatic cyst and found that the cystic fluid was rich in this particular hormone. They have since studied this product extensively and have come to the following conclusions:

- 1 The hormone is present in the blood and is excreted in the urine
- 2 The hormone is present in the blood mainly in an inactivated form and excreted in the urine in its active state
- 3 The active hormone obtained from the urine can be rendered inert by the addition of blood serum
- 4 The inactivated hormone can be reactivated by the addition of acid or a certain vegetable enzyme, papain
- 5 The hormone is not histamine
- 6 The hormone is elaborated and stored mainly in the pancreas
- 7 The action of the hormone is to

cause a drop in blood pressure by means of vasodilation

- 8 The hormone can be used to advantage in patients suffering from angiospastic diseases, coronary sclerosis, and certain forms of hypertension

At the session of the Berliner Medizinische Gesellschaft, July 9, 1930, Frey³ discussed this newly discovered internal secretion and also reported the isolation and purification of a substance, a polypeptide, which inactivates it. "The relation of the link between the hormone and the inactivator is dependent upon the prevailing reaction in the tissues, so that a slight shifting towards the acid side produced by the appearance of acid metabolism releases the link between the hormone and the inactivator, whereby the vasodilator action comes into operation." In this alternation between union and releasing of the active substance—which is brought about by a slight change of the hydrogen ion concentration—Frey sees its real physiologic importance which in connection with internal secretion proves the substance to be a genuine hormone. He also reported the successful use of the hormone for the past two years. "The blood pressure in essential hypertension not caused by the kidneys drops considerably and remains at a lower level after the injections are discontinued. In

*Submitted for publication May 21, 1931

†Read before the Section on Medicine, College of Physicians, Philadelphia, November, 1930

angina pectoris and especially in intermittent claudication the attacks subside. Amputations that in necrosis and gangrene of the extremities would otherwise have been necessary, were avoided, owing to the action of the remedy."

P. Gley and N. Kisthinos⁴, in 1929, prepared a substance from the pancreas which is apparently the same as the one described by Frey and Kraut. They found that the extract had vasodilator properties, was free of insulin in the animal under experimentation, antagonized the action of epinephrine, and caused a transitory hypotension that was not due to choline, histamine, or peptones. H. Vaquez, R. Giroux and N. Kisthinos⁵ have used the product clinically in the treatment of angina pectoris and have reported the most remarkable results. They treated twenty patients in various stages of angina, and in practically every case succeeded in obtaining almost complete symptomatic relief.

Recently J. S. Schwartzman⁶ reported the results of using a voluntary muscle extract in cases of angina pectoris. He explains the favorable effects that he obtained by the presence in the muscle extract of a substance that acts as an antispasmodic, the substance being liberated in a muscle during exercise. M. S. Schwartzman⁷ used the preparation in cases of angina pectoris and also reports very gratifying results. In reference to the antispasmodic substance being found in voluntary muscle only, K. Fahrenkamp and H. Schneider⁸ this past year made a comparative study on man of two extracts, one from skeletal muscle, the other from heart muscle; this latter was previously believed by Haberlandt

to represent a true heart hormone. They found that the effects of the two were identical. Administered either orally or intravenously each of these extracts completely controlled attacks of angina pectoris. The authors concluded that the heart muscle extract does not represent a true heart hormone.

These findings add significance to the work of A. M. Drury and A. Szent Gyorgi⁹. They studied the effect on the heart of simple extracts of heart muscle, and of other body tissues. Some of their conclusions were as follows:

- 1 Simple extracts of heart muscle, brain, kidney and spleen have a definite and transient effect upon the mammalian heart.
- 2 The substance responsible for this action has been isolated and appears from its chemical properties to be adenylic acid. Its activity apparently depends upon the ease with which the substance is deaminated in the body.
- 3 Adenosine, prepared from yeast nucleic acid, had an action identical to adenylic acid.
- 4 The physiological activity of both substances has been tested by intravenous injection into the whole animal.
- 5 Among other effects upon the heart, they slow the rate, impair conduction from auricle to ventricle and arrest experimentally produced auricular fibrillation. They shorten the absolute refractory period of an improved slowed conduction in the auricle due to high rates of beating.
- 6 They lower general arterial pressure. This is due in part to the cardiac slowing and in part

to a general arterial dilatation
They dilate the coronary vessels
and inhibit intestinal movements

We believe that all these substances mentioned are identical, as borne out by our studies, and we are at present making further investigations to prove this

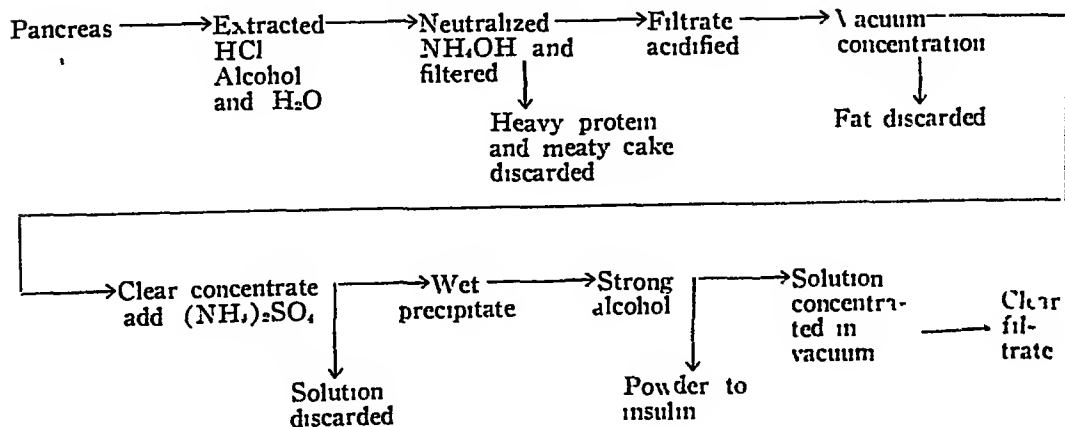
After considering all the experimental and clinical data on the subject, as well as our own work, it seems to us that we are dealing here with an active principle that is either adenylic acid or adenosine. In this connection we want to take cognizance of the editorial in the Journal of the American Medical Association of October 11, 1930. The editor there inclines to the belief that the so-called heart hormone can be obtained in any body tissue and is most likely histamine. While we do not believe that the substance in question is a specific heart hormone, and although it is true that it can be obtained from various body tissues, it nevertheless has definite primary vasodilator properties. It is not histamine as the editor infers. Of this we are quite certain.

We became interested in this product since it is an adjunct in the treat-

ment of angina pectoris and other vascular diseases. We prepared an extract in a manner similar to the method of P. Gley and N. Kisthinos¹⁰. The ground pancreas was extracted with a menstruum of alcohol and water, so that the final alcoholometer reading was 63 per cent. Sufficient hydrochloric acid was used to yield a pH of 2.4. This mixture was run through a colloid mill for thorough extraction. The product was neutralized with ammonia and filtered. This filtrate, acidified with sulphuric acid, was concentrated under vacuum and the clear concentrate sulphated, using ammonium sulphate to one-half saturation. The wet precipitate treated with strong alcohol yielded a powder containing insulin and a 90 per cent alcoholic liquor. This liquor contained alcoholic extractions of the precipitate and the mother liquor wetting it. It was concentrated with the addition of water.

The clear filtrate obtained in the above manner was used for purposes of injection. In making a preparation for oral administration at stage eight, instead of sulphating and collecting the insulin, the product was alcoholized to ninety per cent and then concentrated

FIG. 1 Diagram of method of preparation



We then corroborated the findings antagonized the action of adrenalin and
that it caused a primary drop in arterial slowed the cardiac rate This is seen
pressure when injected intravenously, in the following figures

PANCREAS EXTRACT, LOT "C"
Experiment 568 Ph, 5/21/30

Pancreas Extr, 0.1 cc

Pancreas Extr, 0.075 cc

Pancreas Extr, 0.05 cc

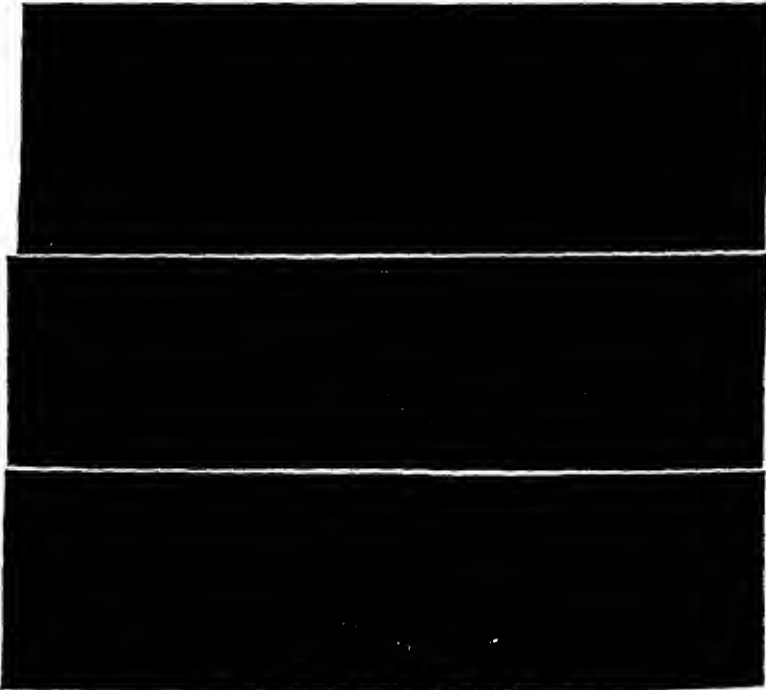


FIG 2—Drop in arterial tension following intravenous injection of vasodilator extract

PANCREAS EXTRACT, LOT "C"
Experiment 568 Ph, 5/21/30

Epinephrine, 10 cc
1:100,000

Epinephrine, 10 cc
Pancreas Extr, 10 cc

Epinephrine, 10 cc
Pancreas Extr, 20 cc

Epinephrine, 10 cc
Pancreas Extr, 40 cc

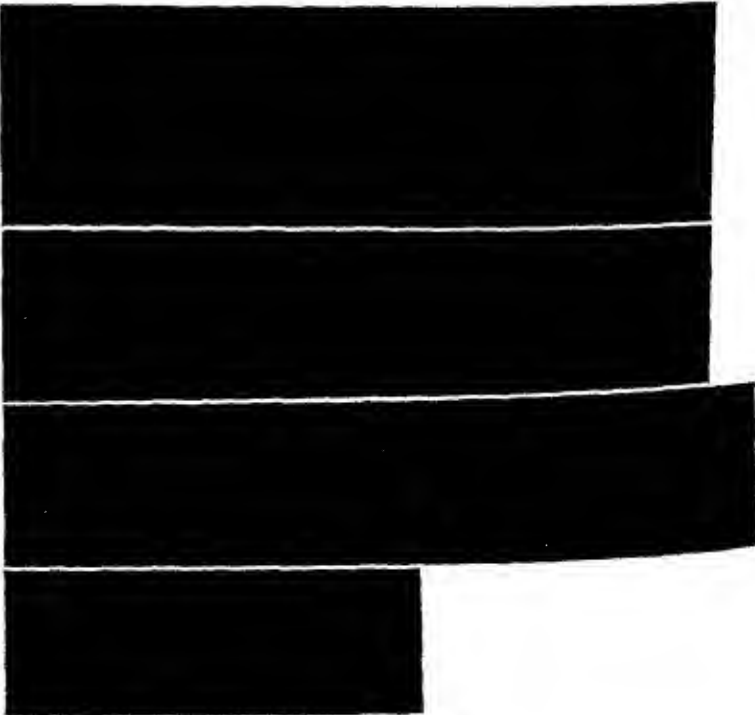
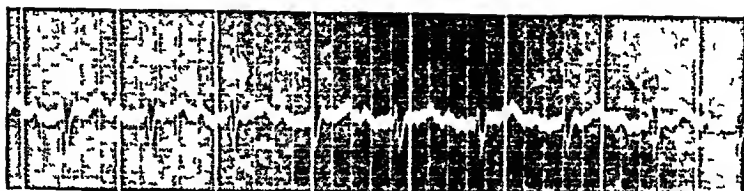
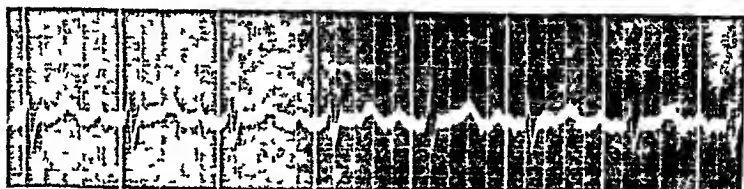


FIG 3—Antagonization of adrenalin effect by vasodilator extract

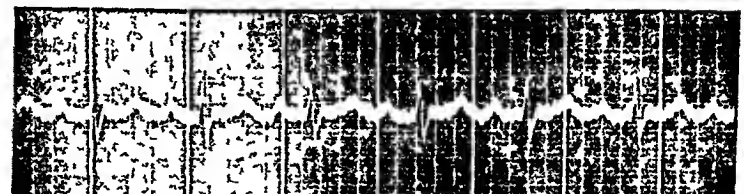
Immediately
after drug
350 per min
R 15
S 70



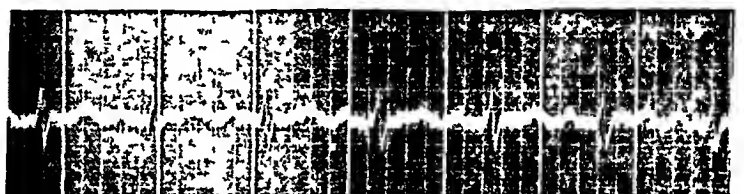
5 min later
280 per min
R 35
S 50



10 min later
252 per min
R 50
S 45



15 min later
252 per min
R 50
S 45



25 min later
228 per min
R 60
S 40

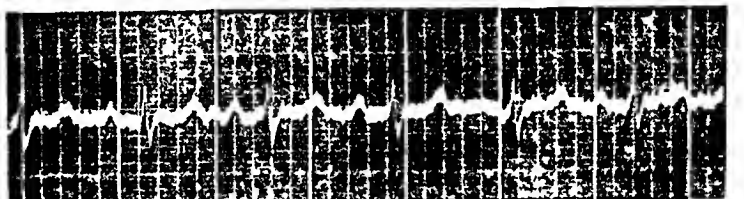


FIG 4 Electrocardiographic tracing of rooster, showing cardiac slowing following injection of vasodilator extract

In order to make sure that the ammonium sulphate used in the process had no hypotensive effect, we administered 0.1 cc of 5 per cent ammonium sulphate. No drop in tension followed.

To rule out the possibility that insulin was responsible for the pharmacologic effect, an injection of 0.75 cc of insulin (20 units) was given. This also failed to cause any appreciable change in blood pressure. To make certain that the animal was still responding, the experiment was concluded with another injection of the vasodilator extract. The result was

similar to the first response, a drop in tension occurring.

We then proceeded to use this vasodilator extract by intramuscular injection.

PREPARATION USED

The extract* which we used, prepared in the above described manner contained 15 hypotensive units per cc. A hypotensive unit according to the method of standardization of P Gley and N Kisthimos¹⁰ is that amount of the extract which when suddenly in-

*We are indebted to Sharpe & Dohme Inc., for their kindness and cooperation in the preparation of the extract.

PANCREAS EXTRACT, Lot "C 2"
Experiment 568 Ph, 5/28/30

0.1 cc of 5% $(\text{NH}_4)_2\text{SO}_4$

Insulin, 20 Unit, 0.075 cc

Pancreas Extr, 1.0 cc

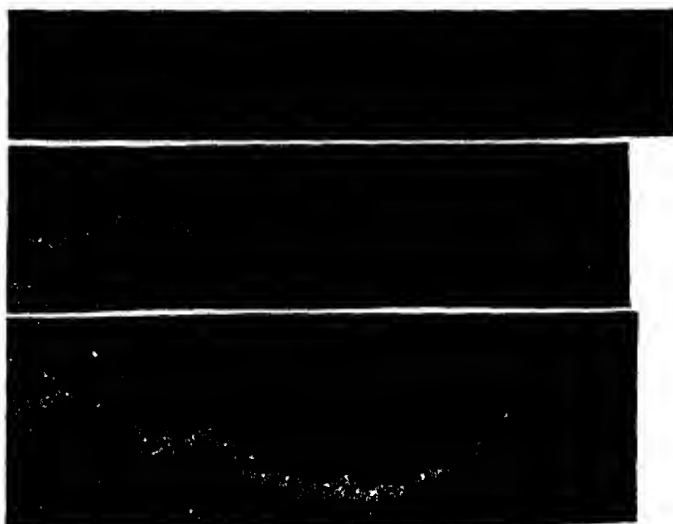


FIG 5—Comparative effect of recording arterial pressure of injections of $(\text{NH}_4)_2\text{SO}_4$, insulin and vasodilator extract

PANCREAS EXTRACT, Lot "C 2"
Experiment 568 Ph, 5/28/30

Pancreas Extr, 0.1 cc

Pancreas Extr, 0.075 cc

Pancreas Extr, 0.05 cc

Pancreas Extr, 0.025 cc

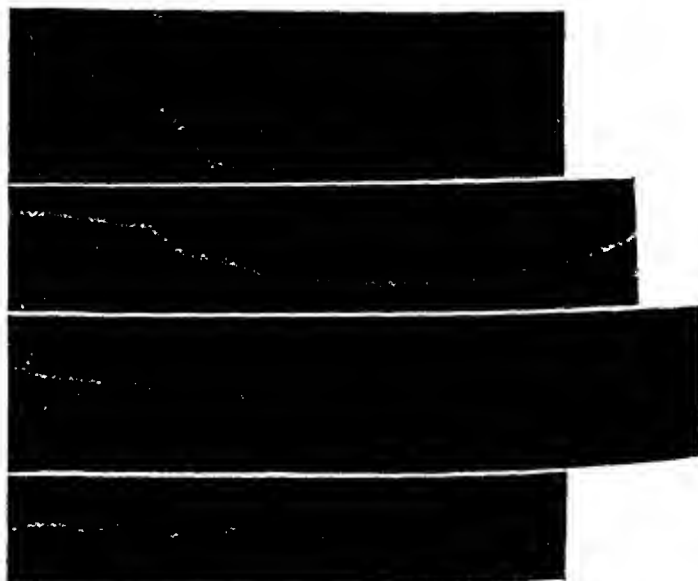


FIG 6—Standardization of vasodilator extract

jected into the jugular vein of a rabbit weighing two kilograms produced a drop in arterial tension just appreciable on the tracing

The experiments that we conducted to determine the toxicity of the extract as indicated in the tables below show it to be nontoxic

TABLE I
DETERMINATION OF TOXICITY OF VASODILATOR EXTRACT

No of Rabbit	Weight Grams	Days	Drug	Kilo Dose	Remarks
5927	2100	0	Vasodilator Extract Intravenously	10 c c per kilo	Normal
	1900	1			Normal
	1880	2			Normal
	1800	3			Normal
	1910	6			Normal
	1870	8			Normal
	1890	9			Normal
	1840	10			Normal
	1940	12			Normal
	1960	15			Normal
	2000	16			Normal
	2090	21			Normal
	Out†				
5934	1600	0	Vasodilator Extract Intravenously	20 c c per kilo	Normal
	1590	1			Normal
	1620	3			Normal
	1670	6			Normal
	1690	7			Normal
	1720	12			Normal
	1740	16			Normal
	Out†				
5936	1910	0	Vasodilator Extract Intravenously	30 c c per kilo	Animal had slight convulsions, was depressed and shaking, breathed heavily and was weak
	1780	1			Normal
	1750	3			Normal
	1830	4			Normal
	1870	5			Normal
	1850	10			Normal
	1890	14			Normal
	Out†				
5937	1900	0	Vasodilator Extract Intravenously	15 c c per kilo	Animal had convulsions, prostrated for 15 min. Later the breathing was heavy and it recovered slightly 30 min later recovered almost completely
	1860	1			Normal
	1840	3			Normal
	1890	4			Normal
	1930	5			Normal
	2010	10			Normal
	2080	14			Normal
	Out†				

†Indicates that the animal was discarded after 2 or more weeks of observation

No of Rabbit	Weight Grams	Days	Drug	Kilo Dose	Remarks
5028	1900	0	Vasodilator Extract Intravenously	25 c c per kilo.	Slight convulsions, re-covered after 3 minutes but was very weak for 30 minutes
	1740	1			Normal
	1730	2			Normal
	1790	5			Normal
	1840	6	Rec'd 15 c c glucose 10%. 5 minutes before extract		Normal
	1850	7			Normal
	1840	8			Normal
	1860	10			Normal
	1810	12			Normal
5050	2010	0	Vasodilator Extract Intravenously	1 25 c c per kilo	No reaction
	2060	1			Normal
	2110	2			Normal
	2160	5	20 c c concentrated down to 2 5 c c		Normal
	2170	6			Normal
	2190	7			Normal
	2220	8	Animal rec'd 15 c c of 10% glucose intravenously 5 min before extract		Normal
	2250	10			Normal
	2210	12			Normal

Our investigation as to the possibility of an anaphylactic action due to the protein that the substance might contain also gave negative results.

SELECTION OF CLINICAL CASES

The cases selected for trial for the purpose had suffered from angina pectoris for a number of years and had failed to respond to all forms of treatment. Nitroglycerin afforded a temporary relief during an attack but did not prevent the recurrence of the attacks. Some were from the New York Hospital, Whitman Memorial Hospital, and our own hospital. The patients were selected for the trial on the basis of

observations were under our own personal supervision. Subjects who had experienced a recent coronary occlusion were rejected. Electrocardiograms and teleroentgenograms were obtained in every case. The whole series had negative blood Wassermanns and negligible urinary findings. Blood pressures were normal in 8 cases and elevated in 12. Cardiac enlargement was present in 14 cases and electrocardiograms showed inverted waves suggestive of supposed coronary disease in 7 cases. Two showed coronar waves during an attack, and two others who had normal electrocardiograms during the beginning of the treatment showed a so-called coronary wave

TABLE II
TEST FOR ANAPHYLACTIC REACTION

No of Guinea Pig	Gram Weight	Days	Drug	Amount	Remarks
1	390	0	Sterile horse serum 1 1,000 made of 1 c c undiluted horse serum plus 99 9 c c salt solution	1 c c 1 1000 solu- tion	
		11	Intraperitoneally	1 c c of un- diluted serum	10 50 A M 10 53 A M animal rest- less and squealing
					11 00 A M scratching mouth with paws
					11 45 A M appeared normal
2	310	0	Sterile horse serum Intraperitoneally	1 c c 1 1000 solution	
		11	Intraperitoneally	1 c c undilu- ted ser- um	Injected 11 25 A M 11 28 animal had chills, be- came restless and squealed 12 00 animal appeared normal
3	350	0	Vasodilator extract 1 1000	1 c c	
		11	Intraperitoneally Intraperitoneally	10 c c undi- luted pancreas extract	Injected 1 49 P M No reaction the animal remained quiet during many hours of observation

ing the time they were receiving the injections. Four of the group had an increased blood pressure during an attack. Three of the patients with a normal pressure at the time of the study were known to have had hypertension at some previous time.

METHOD OF TREATMENT

The method of treatment consisted of daily intramuscular injections, the dosage varying from a minimum of 60 units (4 c c) to a maximum of 150 units (10 c c). The usual dose was 75 units. Where treatment was temporarily stopped the interval before resumption was never more than a week. Every case had been receiving theobromine sodium salicylate, grs 5, acetylsalicylic acid, grs 5, and pheno-

barbital, grs $\frac{1}{4}$, before the injections were started, with some slight favorable effect. This medication was not discontinued when the vasodilator extract therapy was begun. A dose of oleum ricini, 2 oz, was given once every two weeks. Smoking in any form was absolutely forbidden. Instructions were given as to diet and time of meals to avoid any discomfort incident to flatulence. Care was taken to have the patients avoid over-exertion or over-excitement, in other words, we were particular to safeguard against apparently minor disturbing influences.

RESULTS

There was a cessation of the anginal attacks in 11 of the 20 cases. Six others experienced some relief, but

TABLE III
FURTHER CASES

	Age	Sex	Duration of Disease	If present on admission			Evidence of Organic Aortic Change		Effect of Nitroglycerin	Amount of Extract Used Units	Results	Remarks
				Diastolic Pressure	Force of Arterial Wave	Precious History	Cardiac Palpitation	Reent-gon				
I	45	M	10 yrs	0	0	+	0	+	Occasional relief	3000	Free of pain	
II	50	M	10 yrs	0	0	+	0	+	Occasional relief	1620	No relief	Died of coronary thrombosis, decompensated during treatment
III	55	M	2 yrs	+	0	0	+	+	Not used	2160	Free of pain	Able to go about usual duties
IV	57	M	6 mo	0	0	0	0	0	Not used	2000	Partially relieved	Findings mainly subjective
V	57	M	6 mo	+	+	0	0	+	Gave relief	1620	Free of pain	Been taking extract by mouth since
VI	57	M	6 mo	+	0	0	+	+	Not used	1620	Partially relieved	Decompensated during treatment
VII	57	M	2 yrs	0	+	0	+	+	Not used	2160	Free of pain	Been taking extract by mouth since
VIII	58	M	6 mo	0	0	+	+	+	Not used	2400	No relief	Died of coronary attack during coitus Decompensated during treatment.
IX	57	M	4 yrs	+	+	0	+	+	Occasional relief	2700	Free of pain	Died 6 mo after discharge, of coronary thrombosis
X	50	M	3 yrs	0	0	+	+	+	Not used	720	Partially relieved	Auricular fibrillation, refused to continue treatment

[illegible]

still complained of occasional mild paroxysms. In 3 cases the result was a failure.

The following case history is illustrative of the group who were relieved of their anginal attacks.

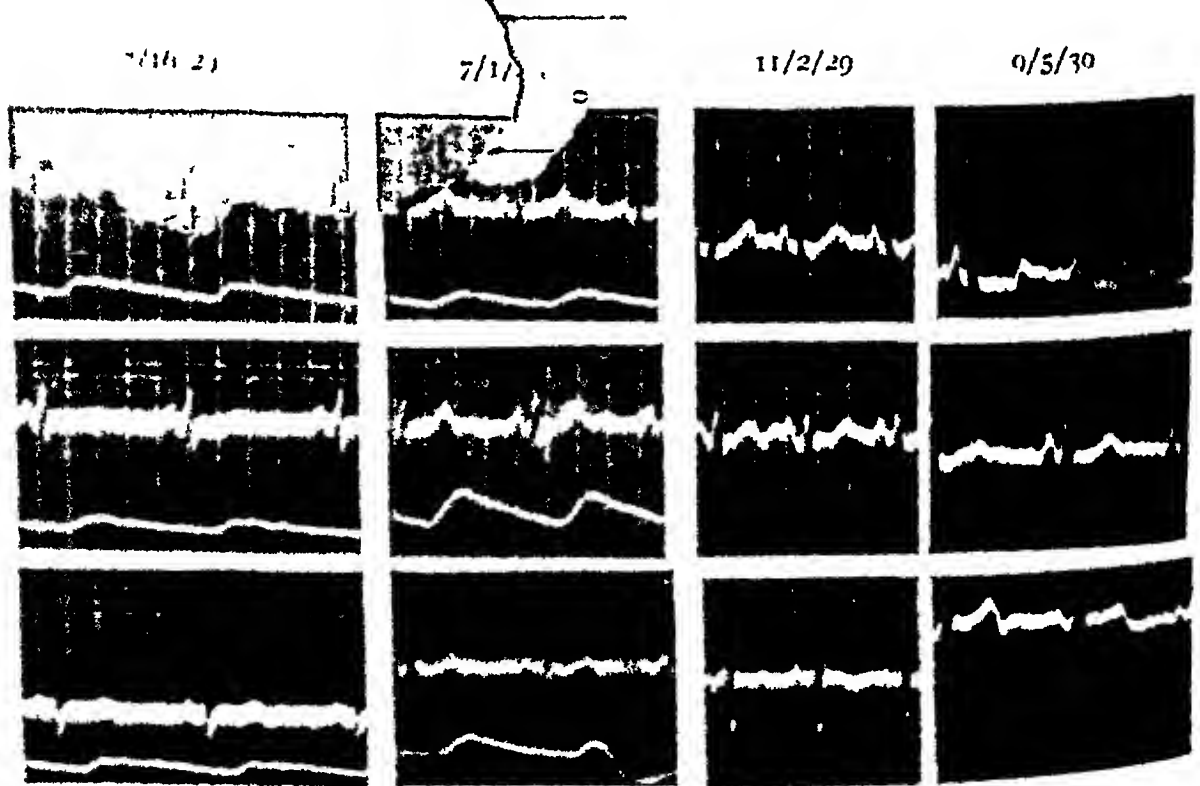
Case 5 M. C., age 50, salesman. The patient was first seen in 1928. He complained of attacks of substernal pain radiating to the throat and left arm. The attacks were precipitated by excitement or exertion and lasted from three to ten minutes. They were occurring about once in two weeks. Although he complained of dyspnea after an attack he never suffered from any respiratory embarrassment at any other time. Upon physical examination we found his heart to be of normal size, the heart muscle tone somewhat muffled, the rhythm and rate were normal. There was a systolic roughening over the aortic area. Blood pressure 180 over 95.

The electrocardiogram revealed the QRS complexes to be of rather low amplitude (figure 7), but otherwise showed no abnormality. The teleroentgenogram showed

the cardiac silhouette to be normal, but the aortic arch was slightly widened and deflected upward and to the left.

The patient was given a combination of theobromine, acetylsalicylic acid, luminal, nitroglycerin, and codeine sulphate. He felt somewhat better but he had two severe attacks at the end of the month. He was then admitted to the hospital where he was given a course of Nauheim baths and injections of sodium citrate. He improved very much in the hospital and after his discharge he had only a few minor attacks until April, 1929. However, tracings taken at intervals showed progressive cardiac damage.

In April the patient suffered several severe attacks of angina and was again admitted to the hospital for a similar course of treatment. This time he felt fairly well until January, 1930. He then had several severe attacks and morphine had to be resorted to. Hitherto nitroglycerin had been effective in controlling the painful crises. The attacks now occurred several times daily. After a week of palliative measures without relief we commenced to give him injections of vaso-dilator extract, 60 units daily, for twelve



days He had no attacks while taking the injections The following week he had a minor attack We then gave him another series of injections, 75 units daily for twelve days He has had no attacks to date He received no more injections but he has taken 60 units by mouth daily since

The following patient also responded very gratifyingly to the vasodilator extract

Case 16, M L, Age 51, machine operator He had been suffering from the subjective symptoms of high blood pressure for three years He was admitted to the hospital in September, 1929, for this condition After being there but a few days he was seized with an attack of excruciating pain over the precordium which left him with a burning substernal sensation He then claimed that he had occasionally experienced similar attacks but much milder in character for over a year His blood pressure ranged between 157 to 200 systolic and 90 to 110 diastolic Teleroentgenogram of the heart showed it to be generally hypertrophied with slight widening of the aorta The patient was in the hospital for three months during which time he had several severe attacks and many minor ones We began giving him the vasodilator extract by injection February 15, 1930, until he had received about 3600 units He has been free from attacks since.

The next history is that of a patient with coronary occlusion whom we succeeded in relieving of her pain, but who died six months after we had ceased treating her

Case 9, G H, age 53, housewife The patient first came under our observation in January, 1928, with a history of a few years' duration, of attacks of precordial pain radiating to both shoulders and to the left arm She also complained of constant headaches and dizzy spells Her blood pressure was 225 over 90 She was sent to the hospital Her teleroentgenogram revealed the heart to be enlarged in its transverse diameter and the aorta to be widened She felt better after a three months' stay in the hospital and a similar period of convalescence at a seaside resort However, as soon

as she returned to her home she began to have attacks Two months later she was hospitalized again

On March 1, 1930, she began to receive daily injections of the vasodilator extract She received in all 2700 units and ceased to have even the slightest attacks She felt so well that she failed to report for observation at appointed times A short time ago we were called to see her and found her moribund from what appeared to be a coronary occlusion A few days later she died

The following is a case of the type that we grouped as being partially relieved

Case 13, A M, age 62, bookkeeper The patient dated her illness to November, 1928, when she suddenly experienced a severe cramp in the epigastrium while walking She was immediately rushed to the hospital where she was treated for acute indigestion At this time it was discovered that she had hypertension and therefore she remained under medical supervision When we saw her she complained also of a sensation of weakness around the heart, dyspnea, and palpitation, and, on excessive exertion, of occasional attacks of excruciating pain in the left shoulder, which would leave her very weak These shoulder pains would be relieved by a hot water bag over the precordium or by drinking hot water In February, 1930, we had her admitted to the hospital for treatment Teleroentgenogram showed the heart to be enlarged in its transverse diameter, and the descending arch of the aorta to be prominent Her blood pressure was 170 over 85

Commencing February 3, 1930, she was given daily injections intramuscularly of vasodilator extract She had one attack after the fourth injection which she claimed was the worst she ever had As a matter of fact we had some difficulty in convincing her to continue with the injections The attack was relieved by 1/100 gr of nitroglycerin She remained in the hospital for two months during which time she received a total of 1600 units During this time she was receiving also theobromine, luminal, and acetylsalicylic acid, and a dose of castor oil every other week We last heard of her

in September, 1930. She claimed that she had been subject to attacks of palpitation and cardiac discomfort, which according to her history seemed to be due to premature beats. She had suffered no definite anginal attacks. Physical examination revealed no change.

The course of events in one of the cases in which the result was a failure, was as follows:

Case 2, S. K., age 63, had not worked for four years due to poor health. The patient was first seen in December, 1929. He was suffering from severe attacks of precordial pain and a strangling sensation, with the radiation of the pain to both shoulders and arms. The patient was extremely ill with marked signs of congestive cardiac failure, and his skin was cold and clammy. He appeared to be much older than his stated age. His blood pressure was 120 over 80. He had been suffering from these attacks for the past eight months but in the last two months they had become progressively worse, until they were unbearable. His doctor had begun to resort to morphine for the last month in order to give him relief. He was removed to the hospital for six weeks and was given a course of Naheim baths. The teleroentgenogram showed his heart to be enlarged in its transverse diameter and the aorta to be calcified.

While in the hospital he did very well, requiring only one hypodermic of morphine during his stay. Until the time of discharge he felt better, but when he went home he continued to have attacks again.

On February 2, 1930, he began to receive the extract of vasodilator extract, 1029 capsules, B. He had no relief during this time, but he developed congestive cardiac failure, which could not be checked in spite of digitalis. Morphine had to be resorted to for relief of precordial cardiac failure.

Summary

1. The extract of vasodilator extract, 1029 capsules, B. has been used in the treatment of angina pectoris in 15 cases. In 10 cases the result was a complete relief of the attacks, and in 5 cases the result was a partial relief of the attacks.

Failure was met with in 15 per cent of the cases. Most patients developed "coronary" "T" waves at the same time that they improved symptomatically (Figures 7 and 8). One patient who suffered from severe intermittent claudication in addition to angina and had been advised to have a sympathectomy performed for the former, was relieved of both complaints by antisymphathone. The four patients who had a rise of blood pressure during an attack were all relieved. Two of the three patients who failed to respond were decompensated at the time treatment was administered. Hence they can be regarded as unfit for trial, since Vaquez also points out the certainty of failure if treatment is undertaken in such instances.

COMMENT

It is our belief that antisymphathone is a valuable addition to the therapeutic armamentarium against angina pectoris. This dread syndrome has long stood invulnerable in very many instances to all methods of treatment. What occasional good results we have hitherto obtained that were more than merely temporary, could never be entirely ascribed to any one drug or therapy. The use of the vasodilator extract promises much better results. To say that it will permanently relieve every case of angina pectoris is to assert a belief that is not warranted by the character of our results or the type that they have endured. But to conclude that it will at least produce some good in half of the cases is a conservative estimate of what we have found. However, we do not believe that the vasodilator therapy is

L K 4/14/30

10/1/30

10/20/30

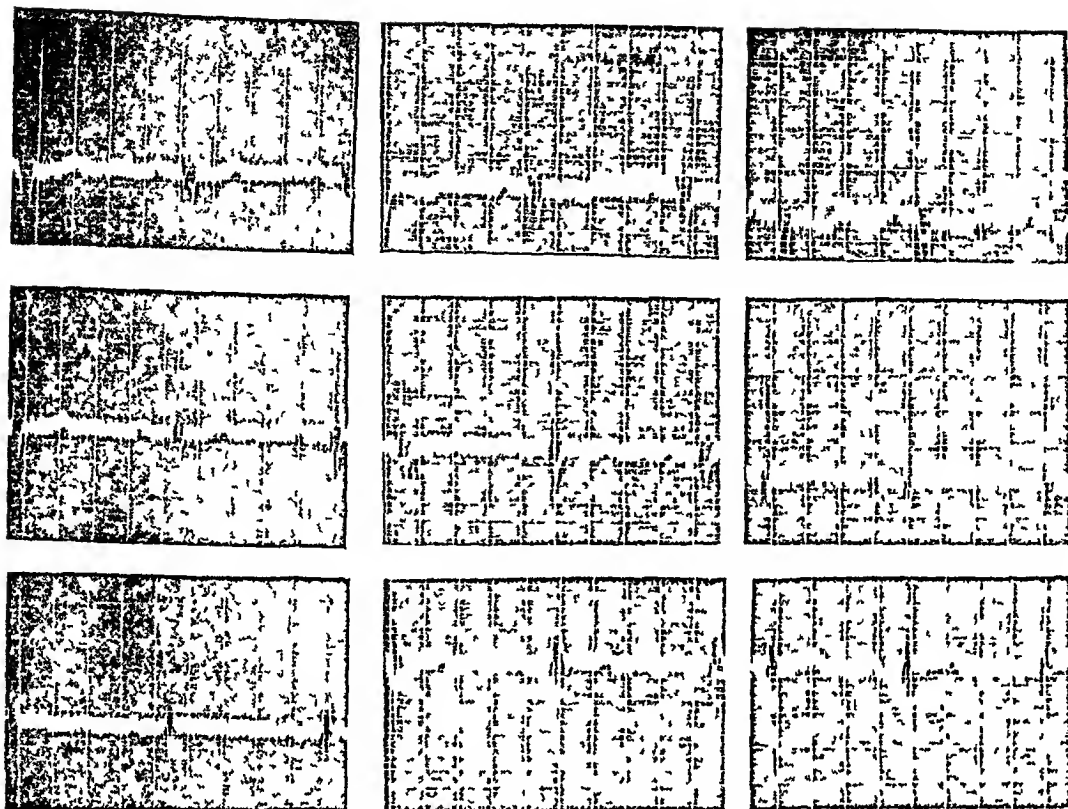


FIG 8—Electrocardiograph, Case XV, showing development of coronary T wave during treatment

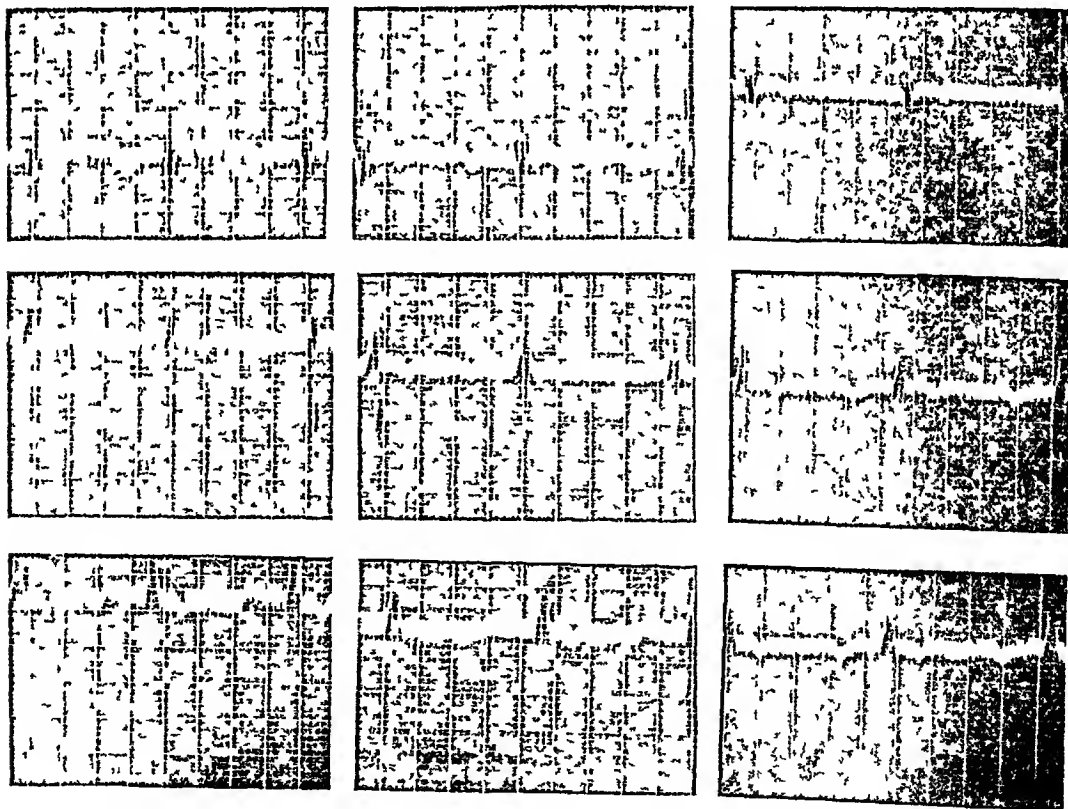
the lesions underlying the anginal attacks. As noted above, one of our patients completely freed of painful crises, experienced a coronary occlusion that was fatal, two others developed coronary "T" waves while under treatment (figures 7 and 8)

A few words at this time as to the *modus operandi* of the extract in relieving angina pectoris would not be amiss. It was the feeling of the French investigators that the beneficial results were due to a trophic action of the extract on the vascular system entirely separate from its hypotensive effects. Several of these patients had no hypertension to begin with and were benefited and several others continued to suffer although their tension was

lowered. We have treated some patients suffering from obliterative arterial diseases of the extremities with this substance and observed improvement. Patients who suffered from intermittent claudication have been greatly benefited by the use of this extract.

Frey's opinion was that all therapeutic benefits derived from the use of the circulation hormone were attributable to its vasodilator action. He mentions good results which he obtained in various angiospastic diseases, coronary sclerosis and hypertension. H. Schauder¹² recently reported the case of a patient who for more than a year had suffered from severe intermittent claudication and arteriosclerosis of the extremities which resisted all therapy.

Fig. 8—Electrocardiograph, Case XV, showing development of coronary T wave during treatment



ly relieved. Failure was met with in 15 per cent of the cases. Most patients developed "coronary" "T" waves at the same time that they improved symptomatically (Figures 7 and 8). One patient who suffered from severe intermittent claudication in addition to angina and had been advised to have a sympathectomy performed for the former, was relieved of both complaints by antisymphathone. The four patients who had a rise of blood pressure during an attack were all relieved. Two of the three patients who failed to respond were decompensated at the time treatment was administered. Hence they can be regarded as unfit for trial, since Vaguez also points out the certainty of failure if treatment is undertaken in such instances.

COMMENT

It is our belief that antisymphathone is a valuable addition to the therapeutic armamentarium against angina pectoris. This dread syndrome has long stood invulnerable in very many instances to all methods of treatment. What occasional good results we have hitherto obtained that were more than merely temporary, could never be entirely ascribed to any one drug or therapy. The use of the vasodilator extract promises much better results. To say that it will permanently relieve every case of angina pectoris is to assert a belief that is not warranted by the character of our results or the time that they have endured. But to conclude that it will at least produce a remission in half of the cases is only a conservative estimate of what we have found. However, we do not believe that the vasodilator therapy removes

was as follows cases in which the result was a failure, The course of events in one of the

change attacks. Physical examination revealed no beats. She had suffered no definite anginal and cardiac discomfort, which according to her history seemed to be due to premature had been subject to attacks of palpitation in September, 1930. She claimed that she

Case 2, S. K., age 63, had not worked for

four years due to poor health. The patient was first seen in December, 1929. He was suffering from severe attacks of precordial pain and a strangling sensation, with the radiation of the pain to both shoulders and arms. The patient was extremely ill with marked signs of congestive cardiac failure, and his skin was cold and clammy. He appeared to be much older than his stated age. His blood pressure was 120 over 80. He had been suffering from these attacks for the past eight months but in the last two months they had become progressively worse, until they were unbearable. His doctor had

resort to morphine for the last month in order to give him relief. He was removed to the hospital for six weeks and was given a course of Nauehm baths. The teleocent- genogram showed his heart to be enlarged in its transverse diameter and the aorta to be widened.

While in the hospital he did very well, requiring only one hypodermic of morphine during his stay. Until the time of discharge he felt better, but when he went home he commenced to have attacks again. On February 3, 1930, he began to receive the injections of vasodilator extract, 1620 units in all. He had no relief during this time and soon developed congestive cardiac failure which could not be checked in spite of stimulation. Morphine had to be resorted to and he died of progressive cardiac failure.

SUMMARY

Thus in 55 per cent of our cases we were able to obtain clinical relief by the use of the tissue extract for which we propose the name "antisymphathone". Thirty per cent were partial-

Treated with Frey and Kraut's circulation hormone the symptoms disappeared almost completely and the good results have persisted for thirteen months

The extract unquestionably has vasodilator properties. Work done on the dog leads us to believe that in this animal at least the primary fall in pressure is followed by a secondary rise. We are at present engaged in testing it on a large group of cases suffering from Buerger's disease and other forms of arterial disease, to determine its clinical applicability. However, it is our belief that the action of the vasodilator extract in relieving angina is associated with its adrenalin neutralizing properties. While the extent of our research on this score only permits us to speculate about it at this time, there are several thoughts that we would like to emphasize.

Sometime ago Levine, Ernstene, and Jacobson¹² showed that an anginal attack could be induced in almost every instance in patients suffering from angina pectoris by the subcutaneous injection of 1 cc of 1 to 1000 epinephrine solution. Control subjects did not experience that reaction.

Loewi¹³ as far back as 1908, experimenting on animals, concluded that the pancreas through an internal secretion (now known to be insulin) furnished a chemical substance which is a depressor or inhibitor of the sympathetic nervous system. The effects of adrenalin, which is a sympathetic excitant, were antagonized or lost. Loewi tried to form a clinical test for pancreatic function from these conclusions, using the reaction of the iris to adrenalin as an index. The applicability and fate

of this test which bears his name is not our concern at this time. The thought that we would like to bring out is that if adrenalin injected into certain patients subject to angina will produce an attack, and if a certain vasodilator obtained from the pancreas moderates the action of adrenalin, a possible explanation of the favorable action of pancreatic extract in relieving angina lies in this very neutralizing property. In other words, antisymphathone acts in the same manner as a sympathectomy. However, some cases of angina pectoris seem to be associated with a preponderance of so-called parasympathetic influences on the heart and other viscera over sympathetic influences. In these cases the use of antisymphathone must be strenuously avoided.

Of course Levine's work does not prove that anginal attacks as they occur in ordinary life are caused by an influx of adrenalin to the circulation. But the frequency of the paroxysms following effort, fright, et cetera, and the common, if not constant observation of the increase in blood pressure during an attack, could readily be explained by an increased adrenalin output in a patient with a damaged cardiovascular system. In fact, as we have just stated, in some cases of angina pectoris parasympathetic influences seem to be predominant.

Whether the injections of antisymphathone stimulate further production of its active principle in the pancreas, or whether the extract acts as a buffer against adrenalin in direct proportion to the amount injected, and whether there is an associated pancreatic disease or deficiency in patients suffering from angina, are questions

that all may be properly asked at this point. Much work and research are necessary before they can be answered, and it is our hope that we have afforded some stimulus to thought and investigation in this direction.

Our purpose in bringing this product to the attention of the profession without any delay is to promote its wide clinical trial. Our work has been far from conclusive. The impossibility of the expression of the locality of pain by animals in the laboratory leaves only the human organism as the means of evaluating the efficacy of the drug. The preparation can be used without further study because of its lack of toxicity. We have administered more than 5000 injections and there has never been any untoward local or general reaction, save a slight burning at the time of injection. It should not, however, be used in cases with parasympathetic preponderance.

Owing to the woeful lack of other than temporary palliatives for anginal crises, we felt assured that the advent of the extract would be welcomed. Our only fear is that the drug may be used with too much enthusiasm and eagerness to allow a proper appraisal of its therapeutic value. It always has been a clinical observation of ours that one's attitude in employing a new therapeutic measure somehow was sensed by the patient and reflected in his or her

reaction. We tried studiously to avoid showing our mental attitude in the hope that where the only measure of our results was the patient's own estimate of his condition, we did nothing consciously to prejudice it.

CONCLUSIONS

1 Twenty cases of angina pectoris were treated with tissue extract (anti-sympathone).

2 Symptomatic relief was obtained in eleven cases, six had partial relief, and three had no relief.

3 We believe that the extract is a valuable addition to the therapeutic armamentarium against angina pectoris, to be used in conjunction with all other means at our command.

4 We believe the mode of action is by sympathetic depression. It should not be used in cases with parasympathetic preponderance.

5 The preparation is non-toxic, its only contraindication being acute coronary thrombosis and the parasympathetic group of cases.

6 We urge wide clinical trial of the extract to better determine its exact value.

Note: We desire to express our indebtedness to Dr. Marie Severac, Mr. R. H. Hutchison, Mr. Arnold Quici, and Mrs. Lena Sklar for their valuable aid in certain phases of this work.

REFERENCES

- ¹FREY, E. K., and KRAUT, H. [Substance stimulating heart activity excreted by the kidney], *Ztschr. f. Biol.*, 1926, LXXXIV, 321-334.
- ²FREY, E. K. Kreislaufhormon und innere Sekretion, *München med. Wchnschr.*, 1929, LXXVI, 1951-1952.

- ³Foreign Letter, *Jr. Am. Med. Assoc.*, 1930, LXX, 676.
- ⁴GIEY, P., and KISTHAKIOS, A. Recherches sur la substance hypotensive du pancreas. *Presse med.* 1929 LXXXII, 1270-1282.
- ⁵VAQUET H., GIBOT, R., and KISTHAKIOS, A. De l'action de certains extraits pan-

creatiques dans le traitement de l'angine poitrine, *Presse méd*, 1929, xxvii, 1277-1279

⁶SCHWARTZMAN, J S Muscle extract in treatment of angina pectoris and intermittent claudication *Brit Med Jr*, 1930, 1, 855-856

⁷SCHWARTZMAN, M S Muscle extract in treatment of angina pectoris and intermittent claudication *Brit Med. Jr*, 1930, 1, 855-856

⁸FAHRENKAMP, K, and SCHNEIDER, H Vergleichende Untersuchungen mit einem als *Hormocardial* bezeichneten Herz-hormonpräparat und einen neuratigen Muskelextrakt, *Med Klin*, 1930, xxvi, 48-50

⁹DRURY, A M, and SZENT-GYORGI Physiological activity of adenine compounds with special reference to their action on

the mammalian heart *Jr Physiol*, 1929, lxxviii, 213-237.

¹⁰GLÉY, P, and KISTHINIOS, N. Recherches sur la substance hypotensive du pancreas, *Presse méd*, 1929, xxxvii, 1279-1282

¹¹SCHAUDER, H.. Zur Behandlung des intermittierenden Hinkens, *München med Wchnschr*, 1930, lxxvii, 196-205

¹²LEVINE, S A, ERNSTENE, A C, and JACOBSON, B M. Use of epinephrin as diagnostic test for angina pectoris with observation on electrocardiographic changes following injections of epinephrin into normal subjects and into patients with angina pectoris, *Arch Int Med*, 1930, xlv, 191-200

¹³LOEWI Sajous, *Analytical Encyclopedia of Medicine*, 10 Edition, Vol 7, Page 268

Medulloblastoma Cerebelli*†

A Case with Autopsy: Midline Cerebellar Tumors in Children and Young Adults

By KARL ROTHSCHILD, M D, *New Brunswick, N J*

BRAIN tumors and especially cerebellar tumors are so frequently seen—and so frequently overlooked—that it seems justifiable to publish a report of some unusual findings in a journal read by the internist. The present paper intends to deal with one phase of the problem, the cerebellar tumors of children and young adults.

In 1925, Bailey and Cushing¹ published an extensive study of these tumors. They report that the initial symptoms were those of increased intracranial tension of abrupt onset, starting only a few months before admission to the hospital. Only occasionally headache was present, usually attributed to some gastric upset. As further symptoms they mention rapid appearance of choked disk, separation of cranial sutures (figures 2 and 3), history of staggering gait, ataxia, more in the lower extremities than in the upper; in a few cases cerebellar seizures with signs suggestive of basilar meningitis. Nystagmus was inconspicuous, diplopia often present, sometimes bilateral abducens palsy. Most cases occurred below the age of

fifteen years. At that time the authors stated that attempts to extirpate these tumors in toto were futile and even exposure and decompression were accompanied by high mortality. "Conservative attitude is a course of wisdom." They recommend decompression followed by persistent roentgen-ray therapy. In 1927 Cushing² reports eleven cerebellar tumors of which the "majority have been median gliomas of one variety or another originating from the roof of the fourth ventricle. Seven of them had a good prognosis." He reports the finding of an enlarged head with MacEwen's sign, the enlargement of the head being followed by cessation of headache and subjective freedom from discomfort but often by that time the vision began to fail. In closing his article he states "Medulloblastoma of the cerebellum is so common a lesion in preadolescence that when a child has unexplained vomiting enlargement of its head and gives a story of periodical instability look at the eye grounds every week or two." Articles by Olivecrona and Ljsholm and by Bailey, Sosman and van Dessel published in 1926 and 1928, show that the growth of the tumors may be inhibited for a time by roentgen therapy but that the outcome has been fatal in every case.

*From the Department of Neuro-Psychiatry, St. Peter's General Hospital, New Brunswick, N J.

†Received for publication March 31, 1931.

Bailey⁵ in his latest article (1930) inquires into the causes of these failures. He rejects the idea that the neoplastic cells may have become radio-resistant. He rather believes that the patients may have received too much roentgen ray treatment. As the method of probable choice he now recommends decompression and thorough radiation of the entire cerebrospinal axis.

Case I The following is a case report of a child, John K., six years of age, who was admitted to my service at St. Peter's General Hospital on May 14, 1930.

Family history Nothing unusual.

Personal history Had chicken-pox at the age of six months, pneumonia at the age of two years, whooping-cough at the age of five years.

Present history Four months before admission the patient fell while skating and struck his head on the ice. He got up and walked home. One week later, he complained of pain in the occipital region of the head and in the abdomen and was taken to see several physicians. Several x-ray pictures were taken and there was a long argument whether a line seen in one of the pictures represented a fracture or not.

About four weeks before admission, the boy complained of dimness of vision, and gradually became blind. On the day of admission, he was seen by Dr. Forney of Milltown, who referred him to my service.

Physical examination A white boy, six years of age, well developed and well nourished, complaining of abdominal pain and apparently blind.

Head and neck Head very large. Veins somewhat large and tortuous. Both pupils were enlarged, round and equal. Right pupil reacted very faintly to light, while left did not react directly, but did so when light was thrown into the right pupil. There was a very slight stiffness of the neck.

Chest Thorax of good capacity, good expansion. Apex beat in 5th interspace, one-half finger breadth within nipple line. Sounds normal, no murmurs. Breath sounds vesicular.

Abdomen Slightly distended, no tenderness, no masses felt.

Extremities Good physical power.

Neurological examination Reflexes.

Tendon reflexes of legs and arms were equal and normal. For a child, they might even be considered below normal. In fact, it was difficult to elicit the arm reflexes at all. Abdominal reflexes were absent. There was an indication of a slight Babinsky's sign on the right side, but nothing definite. There was a suggestion of a bilateral Kernig's sign. There was no ataxia. Finger-finger and finger-nose tests were performed well. The child walked in a straight direction. There was no nystagmus. There were no disturbances of any cranial nerves, except the optic.

Ophthalmoscopic examination Marked optic neuritis in both eyes, with signs of atrophy on the left side. There were many minute ruptures in the retina, showing the sclera, possibly due to suddenly increased pressure. There was also marked choroiditis of the subacute type. The right side was completely blind. The child, however, could notice a flash-light at a distance of four inches with the left eye.

Laboratory findings Hemoglobin, 80%, leukocytes, 9,100, erythrocytes, 4,200,000. Polynuclears, 67%, small lymphocytes, 29%, large lymphocytes, 4%.

Diagnosis In view of the amaurosis, the papilledema, and lack of other localizing symptoms, we made a diagnosis of tumor in the midline of the posterior fossa, probably of the cerebellum.

Progress notes As the child had been in the condition in which he was brought in, for several weeks, there was no indication for hurried therapeutics, so a roentgenogram was ordered to be taken next morning, and dependent on the picture, we considered the possibility of doing a cisternal puncture.

In the morning, the child became rather restless, was crying, and it was impossible to take the roentgenograph. While I was seeing another patient in the children's ward, I was called to see the boy, who had been stricken suddenly by a seizure of not very definite symptomatology. There was frothing at the mouth, incontinence of the rectum,

slight deviation of the eyes to the left, and of the head to the right, absence of reaction of the pupils which were equal and myotic, marked cyanosis of ears and fingers

Heart sounds were irregular and faint, respiration was irregular, of a staccato type, about six per minute

It was deemed advisable to do a spinal puncture. We obtained a clear fluid, under about 12 mm pressure. We removed 1 cc, and the pressure dropped to 7 mm. Cyanosis disappeared, the heart sounds became regular and louder. The respiration, however, did not improve. Withdrawal of 2 cc more, did not help the respiration. 1/20 gr of alphalobelin did not stimulate the respiratory center. The respiration became slower, and ceased entirely within 3 minutes. A cisternal puncture done immediately after death showed fluid of rather viscous consistency, under normal pressure. Immediately after death, we viewed the eye grounds again, and the right eye appeared as before. In the left eye, however, the atrophy of the disks could not be seen so well, because there were acute neuritic changes, with tortuosity of the blood vessels.

Autopsy An autopsy was performed by me with the assistance of Dr Candella. The body was that of a male child of 6 years, well-built and well-nourished, without signs of degeneration or deficiency.

The head appeared much larger than the average, in fact, it was as large as an average adult's head. The circumference was 24½ cm in the longest diameter.

The scalp was removed in the usual way. On removing the skull, it was noticed that the sutures were widened to about 6 mm. Between these sutures, there were two different layers of bone, filling the gaps. It appeared that these insertions had been produced at different times.

The inner aspect of the bone showed many impressions, in fact, there was a true picture of the external architecture of the brain impressed on the bone (convolutional atrophy). Dura was removed easily. Pacchioni's granulations were normal in number, but enlarged. The sinuses within the dura were widened. There were no signs of old or recent infections of the arachnoid or pia membranes.

The brain was removed in toto, by a section which included as much of the oblongate medulla as possible. The weight of the brain was 1425 gms. The external appearance of the brain was normal. Both halves were equal in size. The cerebellum appeared slightly sub-normal in size, but its two halves were equal, and it felt soft throughout. The origins of the cerebral nerves were unobstructed. There was no pathology of the optic tracts. The oblongate medulla showed



FIG 1 Medulloblastoma of cerebellum. Note position in midline. Hemispheres are intact. No localizing symptoms. Natural size.

normal contour and architecture on transverse section

The cortex appeared rather thin. The whole brain had a certain spongy appearance. The usual blood spots seen throughout the white substance were enlarged. The 3rd and 4th ventricles were markedly dilated, especially the 4th. The regions of the striate system and the internal capsule showed normal and regular formations.

On sectioning the cerebellum, a tumor (figure 1) was found of the size of a small hen's egg, originating from the roof of the fourth ventricle. It did not invade the hemispheres of the cerebellum, but only pushed them aside, and the impressions of the tumor were shown on the median aspects of the hemispheres.

The tumor had a spongy appearance, and there were several blood clots found in its interior, apparently originating from a very recent hemorrhage. Histological examination of the tumor proved it to be extremely cellular, without definite arrangement of the cells. In some areas there was pseudo-

rosette formation around a vessel. Mitoses were occasionally seen. There was a scarcity of stroma. The vessels showed proliferative endarteritis. These findings, together with the origin of the tumor from the roof of the fourth ventricle, permitted the diagnosis of a medulloblastoma (figure 4). The tumor was derived from medulloblasts, very young bipotential cells, both spongioblasts and neuroblasts having been found throughout the tumor. (I am indebted to Dr. B. J. Alpers of Philadelphia for looking over the slides and preparing the photomicrograph.)

This case was extremely interesting because there were actually no physical or neurological signs present, except enlargement of the head and slowly increasing amaurosis, the reason being that the hemispheres were not invaded but only pushed aside but well preserved in their outline, as may be well seen in figure 1. This pathology would well corroborate Cushing's description



FIG. 2. Roentgenograph of skull. Arrows point to places of secondary widening of sutures. Note impressions of brain on skull.

of these tumors. If the eye grounds of the child had been examined, the outcome might have been a different one. The law of *post hoc, ergo propter hoc*, certainly led the roentgenologist into over-emphasizing the value of finding a probable fracture. This child showed even fewer symptoms than are generally the rule inasmuch as there were not even vomiting or ataxia

present. Increasing blindness and abdominal pain were the outstanding symptoms. What really caused the unexpected death of the child a few hours after admission to the hospital is not definitely explained. We may assume that there was a sudden hemorrhage into the tumor.

Case II While writing this article I had admitted to my service another child, a boy ten years of age who fell sick with vomiting

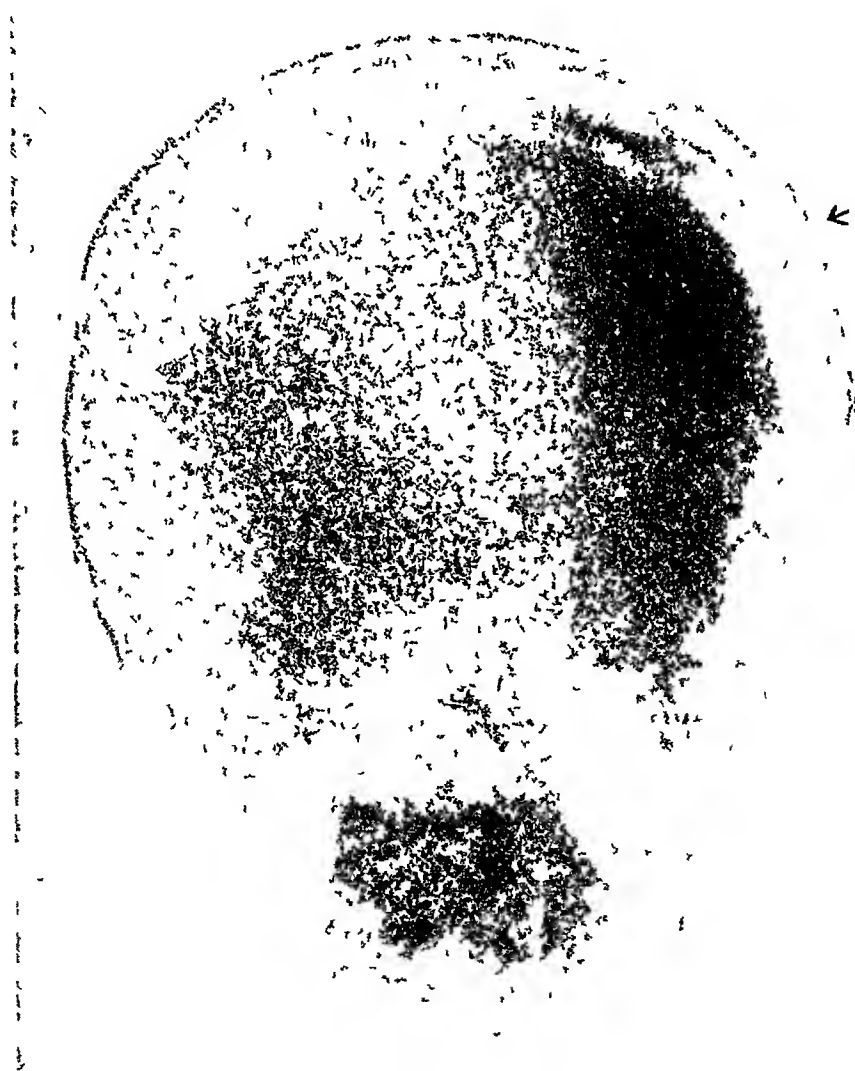


FIG. 3. Antero-posterior view of figure 2.

and dizziness seventeen days ago. On admission to the hospital he showed choked disks and a slight horizontal nystagmus when looking to the right. He felt well while lying down. The deep reflexes were abolished, with possible presence of diminished left Achilles reflex and an indication of positive Babinsky's sign on the left. Finger-finger, finger-nose, and heel-knee tests were normal. Romberg's sign was positive. When sitting up, the patient became very dizzy and vomited. In this case also, I made a diagnosis of a tumor in the posterior fossa, invading the left hemisphere.

A few days after admission, the child felt considerably better, and was able to stand up and walk. He remained free from dizziness and headache. Only the choked disks remained unchanged. But after five days more, the former symptoms returned, the vision became dim and diplopia developed. The family physician later told me that

there had been diplopia for two days prior to admission to the hospital.

We now had the child admitted to the neuro-surgical department of the University of Pennsylvania. Dr. Charles H. Frazier kindly reported to me that he performed the operation, after having made a diagnosis of lesion of the posterior fossa, probably involving the left cerebellar hemisphere. The operation was performed under colonic and avertin anesthesia. The posterior horn of the left ventricle was tapped and a large quantity of fluid escaped. After transverse incision, the occipital sinus was ligated. The various surfaces of the left cerebellar hemisphere were explored with negative results. No difference in size of the hemisphere was noted and no displacement of the midline. An exploratory canula was introduced into the left hemisphere with negative results.

"For these several reasons, chiefly because of the lack of displacement of the midline,

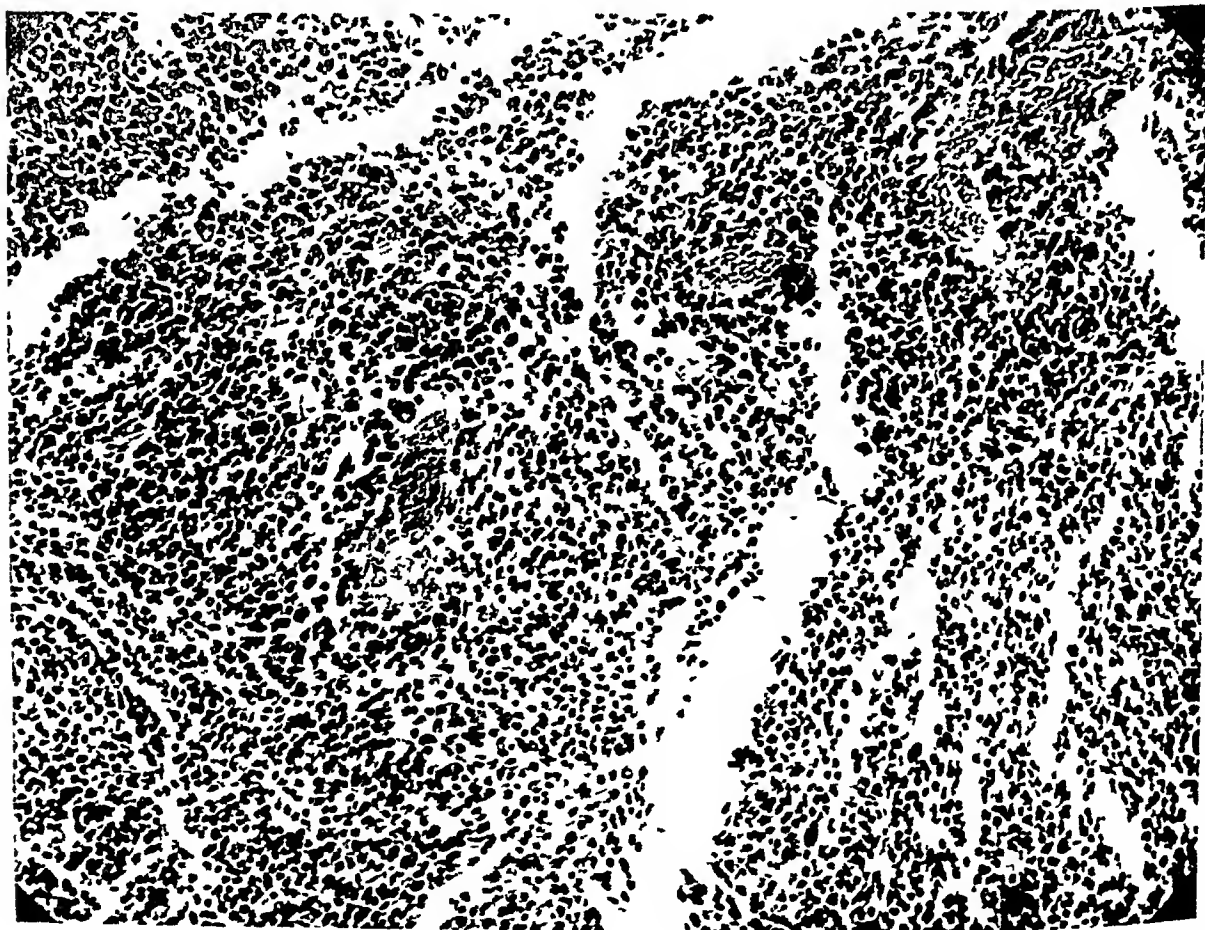


FIG. 4. Microphotograph of tumor (Case 1). Extremely cellular. Tendency to grouping of cells around blood vessels. Occasional mitoses in nuclei. Stroma sparse. (Medulloblastoma)

because the two hemispheres were of equal size, because of the extensive amount of fluid in the subarachnoid space and in the ventricles, I was disposed to regard the case as one of pseudo-tumor. It is possible, I suppose, that there may be a neoplasm of the fourth ventricle but the evidence did not seem sufficient to warrant incision of the vermis" (Dr Frazier)

To judge from the history of the case, the free interval after an acute attack and the appearance of the roentgen plates, I am rather inclined to believe that we are dealing with a tumor. The description of Case I shows that there was in this case also no displacement of the midline, that the hemispheres were equal in size and that there was no evidence to touch of the presence of a tumor. Further developments will clear up this case. What is important from the standpoint of this paper, however, is that the diagnosis of a tumor (or a pseudo-tumor) over the original one of encephalitis was the point which decided whether this child should become blind or not. In either case, the diagnosis of involvement of the posterior fossa (by tumor or localized arachnitis) could be made from not much more than an eye ground examination.

Case III A similar case came under my observation on April 5, 1930. The patient, Norman R., a clerk of 24 years of age, had fainted while walking in the street, had fallen, and was taken to St Peter's Hospital. After admission, he vomited for several hours. The history dates back four years. Similar fainting spells had occurred every few months, each time while the patient was taking a walk. All attacks were accompanied by vomiting. A day or two after each attack the patient felt well again.

Neurological examination showed slight exaggeration of left biceps and triceps and absence of left abdominal reflexes. No a-

taxia of upper extremities. Tendency to sway toward the left when walking. Slight weakness of the left abducens. Eye grounds showed dilatation of blood vessels and choking of the disks, a little more marked on the left.

Diagnosis Cerebellar tumor (in midline)

In this case, also, the patient improved within a few days and left the hospital in apparently good condition. I saw him four months later and he was feeling well. He refuses to be examined again, for fear, apparently, that our original diagnosis might be verified.

All of these cases had been treated before, and diagnosed as fracture of the skull (case I), encephalitis (case II) and gastric upset (case III). Judging from these experiences, it may be well to follow Cushing's advice and in cases of recurrent vomiting and dizziness, examine the eye grounds every week or two.

The material described in this paper was presented at the Scientific Exhibit of the American Medical Association at the Philadelphia session, June 1931.

References 6 to 14 represent the latest investigations on the subject.

CONCLUSIONS

1 Tumors of the cerebellum, especially medulloblastomata, are found relatively frequently in children and young adults.

2 The onset of the symptoms of medulloblastoma in this region is so insidious, and the symptoms themselves are so slightly specific that the practitioner should be directed toward considering such a tumor in cases of dizziness and vomiting of indefinite origin. Choked disks are an early sign.

3 Three cases are described, one with report of autopsy.

REFERENCES

- ¹BAILEY, P, and CUSHING, H Medulloblastoma cerebelli, Arch Neurol and Psychiat, 1925, xiv, 192-224
- ²CUSHING, H The intracranial tumors of pre-adolescence, Am Jr Dis Child, 1927, xxxiii, 551-584
- ³OLIVECRONA, H, and LYSHOLM, E Notes on roentgen therapy of gliomas of brain, Acta radiol, 1926, vii, 259-268
- ⁴BAILEY, P, SOSMAN, M C, and VAN DESSEL, A Roentgen therapy of gliomas of brain, Am Jr Roentgenol, 1928, xix, 203-264
- ⁵BAILEY, P Further notes on the cerebellar medulloblastomas, the effect of roentgen radiation, Am Jr Path, 1930, vi, 125-136
- ⁶SACHS, E The diagnosis and treatment of brain tumors, 1931 Mosby, St Louis, 157-159
- ⁷BERTRAND, I, and GIROT, L Tumeur du lobe droit du cervelet (médulloblastome), Rev Neurol, 1929, i, 245-248
- ⁸GRANT, F C Clinical study of midline cerebellar tumors in children, Surg Clin North America, 1929, ix, 1155-1168
- ⁹CUSHING, H Experiences with cerebellar medulloblastomas, critical review Acta path et microbiol, Scandnav, 1930, vii, 1-86
- ¹⁰GUILLAIN, G, BERTRAND, I, and PÉRISON, J Médulloblastome du quatrième ventricule à évolution aigue, Rev neurol, 1930, ii, 62-66
- ¹¹WOHLWILL, F Zur pathologischen Anatomie der malignen Kleinhirntumoren der Kinder (sog "Medulloblastome"), Ztschr f d ges Neurol u Psychiat, 1930, cxxviii, 587-614
- ¹²ALAJOUANINE, DE MARTEL, and GUI-LAUME Deux médulloblastomes du quatrième ventricule (ablation, guérison opératoire), Les troubles pseudo-digestifs initiaux des tumeurs de la fosse postérieure, Rev neurol, 1930, ii, 94-100
- ¹³MARBURG, O Zur Kenntnis des sogenannten Medulloblastoms (Sphaeroblastoma polymorphon), Deutsche Ztschr f Nervenhe, 1931, v, 117-119 289-308
- ¹⁴VAN GEHUCHTEN, P, and MORELLE, J Deux cas de tumeur du cervelet Quelques réflexions au sujet du syndrome cérébelleux de la ligne médiane, Jr de neurol et de psychiat, 1930, xxi, 866-871

Electrocardiographic Studies of the Effects of Propylene as a General Anesthetic in Man*

By MORRIS H. KAHN, M.A., M.D., F.A.C.P., and LLOYD K. RIGGS, Ph.D.,
New York City

THE effects of propylene, an unsaturated hydrocarbon of the olefine series, as an anesthetic in animals have been reported in a number of communications by Halsey^{4,5,6} and his coworkers, by Riggs^{1,2,3} and Goulden³ and by others, with interesting and encouraging results. All have reported that propylene was an effective anesthetic in concentrations of 40 to 60 per cent by volume. None of these authors have reported either an immediate or delayed toxic action of this hydrocarbon. It appeared, therefore, that propylene might with safety be tried out in actual surgical practice.

A group of research workers in New Orleans under the leadership of Prof. Halsey of Tulane University were the first to undertake clinical trials of propylene. Two cases of appendectomy were reported, in one of which marked irregularity of the heart developed toward the end of the period of anesthesia which was maintained for a little over thirty minutes.

Gwathmey, of New York, reported the use of propylene as an anesthetic for short dental operations, and observed no unfavorable heart symptoms.

Caine⁸ and Reynolds^{8,9} undertook

electrocardiographic studies on the action of propylene and other anesthetic gases. They found that non-anesthetic concentrations of propylene (25 per cent) caused ectopic ventricular beats which promptly disappeared when the concentration of propylene was lowered. Higher concentrations of propylene caused more frequent ectopic ventricular beats and runs of ventricular tachycardia of longer or shorter duration.

Chapman studied the action of propylene and of ethylene upon isolated turtle and frog hearts and found that "propylene in narcotic dosage is somewhat less depressing to these cold-blooded hearts than is ethylene."

In view of the above evidence Riggs and Goulden pursued further their studies on the physiologic action of propylene, giving special attention to its action upon the heart, and studying carefully the mechanism of death, watching the time of the cessation of respiration and of the heart beat. They employed cats, dogs, guinea-pigs and rabbits. Their results tended strongly to confirm their previous observations that the primary toxic action of propylene is upon the respiratory center, and quite secondarily upon the heart.

*Submitted for publication, April 15, 1931.

METHOD OF ELECTROCARDIOGRAPHIC STUDY

In view of these studies it appeared desirable to proceed with electrocardiographic studies on the human subject under propylene anesthesia. Dr Lloyd K. Riggs offered himself as the subject of these experiments which were carried out at the Beth Israel Hospital in New York City. Dr Riggs submitted himself to general anesthesia two or three times each day that the experiments were conducted, at intervals sufficient to permit the dissipation of any possible overhanging effects from one period of anesthesia to the next. The experiments were conducted at weekly intervals, and the anesthetic was administered two or more hours after a light meal but with no other preparation.

A length of rubber tubing held in the patient's hand was connected to a tambour and indicator which swung in front of the slit of the camera of the electrocardiograph. This was used to indicate each inspiration of the patient until he became unconscious, and again his respirations when he remembered to signal as he recovered from the anesthetic.

At first continuous records were taken in either Lead I, 2 or 3 as indicated in the tables. Subsequently it was considered equally adequate, during more prolonged anesthesia, to take short strips of record at definite intervals of one-quarter to one minute. Very careful analyses were made of the electrocardiographic films under the following headings:

1 The intervals between respirations, from the first exhibition of the

anesthetic until anesthesia was complete.

2 Adding these, we ascertain the length of time it required for propylene to anesthetize the patient.

3 The R-R interval in seconds indicates the rate of the heart beat in very exact figures.

4 The P-R interval indicates the conduction period in the heart and suggests the central nervous effects of propylene upon the heart mechanism.

5 Other miscellaneous effects, if and as they are encountered.

METHOD OF ANESTHESIA

Propylene had been freshly prepared the day previous to the experiments in various concentrations and was administered under atmospheric pressure by displacement with water. At first it was used in a freshly prepared mixture consisting of propylene 40 per cent, oxygen 20 per cent and the rest nitrogen. This applies to Experiments 1 and 2. In Experiments 3, 4 and 5 we used propylene 50 per cent, oxygen 20 per cent and nitrogen 30 per cent. In experiment 6 we used 75 per cent propylene and 25 per cent oxygen. In Experiments 7, 8, and 9 we used 50 per cent propylene, 20 per cent oxygen and 30 per cent nitrogen.

In every case the anesthesia was maintained for a period of a few minutes, and in the last experiment it lasted 16 minutes.

GENERAL EFFECTS OF THE ANESTHETIC

During administration of propylene, in all but the last experiment, the respirations continued entirely regular as is indicated in the tables by the time

intervals between respirations After the first few breaths, there was usually slight reddening of the eyelids with some lacrimation and flushing of the face This was more marked with a high concentration of the anesthetic Apparently the irritation was more than conjunctival as sometimes coughing would occur from pharyngeal irritation Just before the patient became unconscious there was noted contraction of the left leg and sometimes

also flexion of the right leg which quickly subsided and the legs would remain entirely limp Otherwise the progress of the anesthesia was uneventful and gradual, and after an average period of ten breaths anesthesia was complete During this time pinching or sticking the patient with a pin indicated complete insensitiveness The tables 1 to 9, show the rapidity with which the anesthesia produced unconsciousness

TABLE I
ANALYSIS OF EXPERIMENT I

Progress of the Experiment	Duration of Signal	Intervals between Inhalations	R-R Interval	Heart Rate	P-R Interval
Before Signal			6-72	83-100	16 sec
1st Inhalation	14 sec	70 seconds	6-66	91-100	
2nd "	9 "	70 "	6-68	88-100	
3rd "	20 "	70 "	7-65	86-92	
4th "	18 "	70 "	6	100	
5th "	9 "	70 "	6	100	16 "
6th "	4 "	60 "	56	107	
7th "	4 "	55 "	56	107	
8th "	2 "	60 "	56	107	
9th "	7 "	51 "	56	107	
Anesthesia complete after 57.6 seconds					
During Anesthesia			56	107	16 "
Recovering from Anesthetic-Onset			6-66	91-100	14 "
After ½ minute			6-66	91-100	16 "
After 1 minute			68-72	83-88	20 "
After 2 minutes			76	79	20 "
Remarks	Lead 3 used Pulse was good and unchanged throughout Face flushed Recovering signal given by patient 1 minute after removal of mask, duration of signal was 0.6 second Propylene 40%, Oxygen 20%, and Nitrogen 40%				

TABLE II
ANALYSIS OF EXPERIMENT II

Progress of the Experiment	Duration of Signal	Intervals between Inhalations	R-R Interval	Heart Rate	P-R Interval
Before Signal			68	88	14 sec
1st Inhalation	12 sec	36 seconds	7	86	
2nd "	19 "	52 "	68	88	
3rd "	20 "	50 "	66	91	
4th "	24 "	52 "	64	93	
5th "	10 "	46 "	64	93	
6th "	6 "	56 "	68	88	16 "
7th "	2.4 "	56 "	64	93	
8th "	26 "	50 "	64-68	88-93	
9th "	20 "	54 "	68	88	16 "
10th "	22 "	50 "	68	88	
11th "	22 "	54 "	64-72	83-93	
12th "	24 "	94 "	68	88	
Anesthesia complete after 65.0 seconds					
During Anesthesia			72-78	77-83	
Recovering from Anesthetic-Onset			72	83	16 "
Signal after ½ minute			70	86	
Remarks	Lead 2 used Propylene 40%, Oxygen 20%, Nitrogen 40% Recovering signal given by patient ½ minute after removal of mask, duration of signal 1.6 second				

TABLE III
ANALYSIS OF EXPERIMENT III

Progress of the Experiment	Duration of Signal	Intervals between Inhalations	R-R Interval	Heart Rate	P-R Interval
Before Signal			64-68	88-93	16 sec
1st Inhalation	22 sec	50 seconds	8	75	16 "
2nd "	18 "	50 "	7	86	
3rd "	20 "	52 "	66	91	
4th "	12 "	44 "	68	88	16 "
5th "	30 "	60 "	64	93	
6th "	36 "	72 "	6	100	16 "
7th "	22 "	52 "	6	100	16 "
Anesthesia complete after 38 seconds					
During Anesthesia			56-6	100-107	16 "
Recovering from Anesthetic-Onset			64	93	16 "
Signal after ½ minute			72	83	
After 1 minute			72	83	
Remarks	Lead 2 used Propylene 50%, Oxygen 20%, Nitrogen 30% First return of consciousness was indicated by the signal				

TABLE IV
ANALYSIS OF EXPERIMENT IV

Progress of the Experiment	Duration of Signal	Intervals between Inhalations	R-R Interval	Heart Rate	P-R Interval
Before Signal			74-78	77-81	14-16 sec
1st Inhalation	08 sec	40 seconds	72	83	14 "
2nd "	04 "	50 "	74	81	
3rd "	10 "	50 "	68	88	14 "
4th "	04 "	52 "	68	88	
5th "	06 "	50 "	60-64	93-100	16 "
6th "	06 "	48 "	60	100	16 "
7th "	04 "	46 "	60-62	97-100	
Anesthesia complete after 33.6 seconds					
During Anesthesia			66	91	14-16 "
Recovering from Anesthetic					
Signal after ½ minute			62-66	91-97	14-16 "
1 minute after			76	79	14 "
Remarks	Lead 2 used Complete anesthesia was maintained for about two minutes Propylene 50%, Oxygen 20%, Nitrogen 30%				

TABLE V
ANALYSIS OF EXPERIMENT V

Progress of the Experiment	Duration of Signal	Intervals between Inhalations	R-R Intervals	Heart Rate	P-R Intervals
Before Signal			68-72	83-88	14-16 sec
1st Inhalation	16 sec	56 seconds	72	83	16 "
2nd "	10 "	52 "	76	79	
3rd "	20 "	56 "	64	93	16 "
4th "	20 "	54 "	62	97	16 "
5th "	16 "	56 "	60	100	
Anesthesia complete after 27.6 seconds					
During Anesthesia			58-60	100-104	14-16 "
Recovering from anesthetic after 1 minute			74-80	75-81	14-16 "
Remarks	Lead 2 used Propylene 50%, Oxygen 20%, Nitrogen 30%				

TABLE VI
ANALYSIS OF EXPERIMENT VI

Progress of the Experiment	Duration of Signal	Intervals between Inhalations	R-R Intervals	Heart Rate	P-R Intervals
Before Signal			72	83	16 Sec
1st inhalation	10 sec	52 seconds	72	83	
2nd "	26 "	52 "	68	88	
3rd "	22 "	56 "	68	88	16 "
4th "	24 "	54 "	72	83	16 "
5th "	20 "	56 "	72	83	16 "
6th "	30 "	68 "	72	83	
7th "	24 "	64 "	72	83	
8th "	28 "	66 "	70	86	16 "
9th "	26 "	70 "	68	88	
10th "	24 "	60 "	70	86	
11th "	24 "	60 "	72	83	16 "
12th "	30 "	62 "	64	97	
13th "	24 "	52 "	7	86	
Anesthesia complete after 77.2 seconds					
During Anesthesia			68	88	16 "
Recovering from Anesthetic-Onset			76	79	16 "
	½ minute after		72	83	16 "
	1 minute after				
1st signal	16 sec	50	76-82	73-79	
2nd "	16 "	52	71-76	79-81	
	2 minutes after				
	3 minutes after		72	83	
	4 minutes after		72-76	79-83	16 sec
Remarks	Lead 2 used Propylene 75%, Oxygen 25% There were slight twitches of the left leg and right shoulder and movements of the head then swallowing movements and watering of the conjunctivae				

TABLE VII
ANALYSIS OF EXPERIMENT VII

Progress of the Experiment	Duration of Signal	Intervals between Inhalations	R-R Intervals	Heart Rate	P-R Intervals
Before Anesthesia Leads 1, 2, 3			72-76 sec	79-83	14 sec
Before Signal			64 "	93	12-16 "
1st Inhalation	08 sec	50 seconds	64	93	
2nd "	10 "	60 "	68	88	
3rd "	06 "	54 "	70	86	14 "
4th "	16 "	52 "	68	88	
5th "	16 "	62 "	64-66	91-93	14 "
6th "	28 "	62 "	62	97	
7th "	20 "	66 "	60	100	12-14
Anesthesia complete after 40.6 seconds					
During Anesthesia—after ½ minute			64	93	12-14 "
" 1 minute			70-72	83-86	14 "
" 2 minutes			85	71	12
" 3 minutes			76	79	14
" 4 minutes			70	86	
" 5 minutes			68	88	
Recovering from Anesthetic—First signal			84	77	14 "
After 1 minute			80	77	14
Remarks	Lead 2 used Propylene 50%, Oxygen 20% Nitrogen 30%				

TABLE VIII
ANALYSIS OF EXPERIMENT VIII

Progress of the Experiment	Intervals between Inhalations	R-R Intervals	Heart Rate	P-R Intervals
Before Signal		74-76	81-83	14 sec
1st Inhalation	60 seconds	68	88	
2nd "	60 "	64	93	
3rd "	66 "	66	91	
4th "	62 "	64	93	14 "
5th "	62 "	60	100	
Anesthesia complete after 40 seconds				
After 1 minute		60	100	14 "
" 2 minutes		68-70	86-88	16 "
" 3 "		72	83	16 "
" 4 "		76-82	73-83	
" 5 "		80-84	72-75	
" 6 "		84-92	65-85	14 "
Recovering from Anesthetic				
First Signal		72-74	81-83	
After 1 minute		72-74	81-83	
Remarks	Lead 2 used Propylene 50%, Oxygen 20%, Nitrogen 30%	During complete anesthesia strips of record were taken at intervals of one minute until patient regained consciousness		
		64-68	88-93	16 sec

TABLE IX
ANALYSIS OF EXPERIMENT IX

Progress of the Experiment	Intervals between Inhalations	R-R Intervals	Heart Rate	P-R Intervals
Before Signal		72	83	14 sec
1st Inhalation	50 seconds	76	86	
2nd "	50 "	72	83	
3rd "	60 "	72	83	
4th "	66 "	72	83	
5th "	44 "	66	91	
6th "	48 "	68	88	
7th "	48 "	68	88	
8th "	58 "	64	91	14 "
Anesthesia complete after 42 1/2 seconds				
During complete anesthesia-Onset		68	88	14 "
After 1 minute		70-76	81-86	
" 2 minutes		82	73	
" 3 "		84	72	
" 4 "		86	70	
" 5 "		76	81	
" 6 "		78	77	
" 7 "		74-76	81-83	
" 8 "		78	77	
" 9 "		78-80	75-77	
" 10 "		78-80	75-77	
" 11 "		78-82	73-77	
" 12 "		84	72	
" 13 "		84	72	
" 14 "		80-92	65-75	
" 15 "		76	81	
" 16 "		76-80	75-81	
Patient suddenly ceased to breathe for 40 to 60 seconds, then he gasped, and soon recovered				
The heart beat remained unchanged				
Recovering from the Anesthetic		80	75	14 "
Remarks	Lead 2 used Propylene 50%, Oxygen 20%, Nitrogen 30%	Depression of the respiratory center occurred with cessation of breathing for about one minute, while the heart beat was not appreciably affected		

During anesthesia in all but the last experiment the patient's breathing continued regular. There was no further lacrimation nor any movement of skeletal muscles until the commencement of recovery from the anesthetic. With that, the patient gradually opened his eyes, looked about him, smiled, swallowed, drew his right hand up to his mouth with a motion as if to wipe his lips, and felt for the tubing of the signal to press, that being apparently the prompt recollection. The return of the signal on the film was a suitable indication of returning consciousness. There was no feeling of nausea or vomiting during any of the experiments, and no feeling of any illness at all. After a maximum of two minutes from the removal of the anesthetic, consciousness was complete. The patient desired to sit up and inquired how the anesthesia had progressed.

ELECTROCARDIOGRAPHIC EFFECTS OF PROPYLENE

A preliminary electrocardiographic study was made before each experiment to ascertain the normal status of the individual. The electrocardiogram of Dr. Riggs was entirely normal, with moderate voltage, showing all the waves upright in the three leads, of normal duration and normal time relations, and fairly well marked sinus arrhythmia.

During the progress of the anesthesia the sinus arrhythmia became less distinct. We consider this, as shown by the graph (figure 1), a quite definite effect of propylene. In no experiment was there evidence of any sudden change of rate, except that resulting from the lessened sinus arrhythmia. In each of the experiments, when the patient aroused from the anesthesia, the pulse rate was two to ten beats lower.

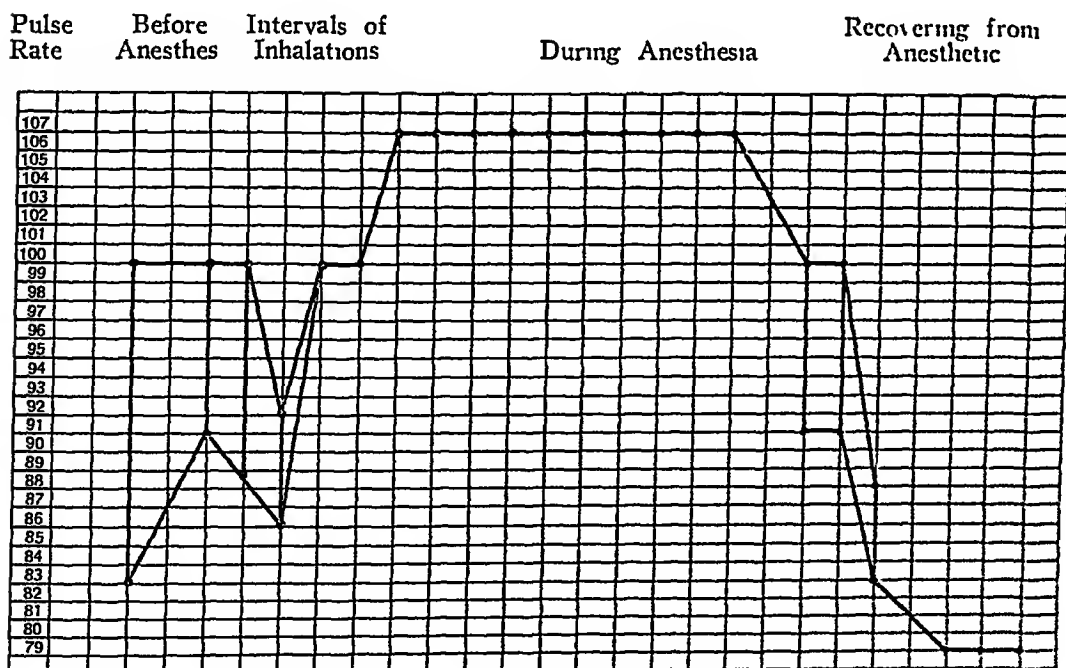


FIG 1
Graph showing the effect of propylene anesthesia on sinus arrhythmia
(From experiment 1)

than at the beginning of the anesthesia. The rate and the sinus rhythm returned to their original status within a few minutes after recovery from anesthesia. The character of the waves and the voltage remained unchanged during the experiments. No aberrant conduction tract was noted in any films, and no premature beats or any other form of irregularity occurred.

SUMMARY AND CONCLUSIONS

Electrocardiographic studies were made on the human subject of the effects of propylene as a general anesthetic. From their previous experimental work with animals Riggs and Goulden had come to the conclusion that the primary toxic action of propylene is upon the respiratory center, and quite secondarily upon the heart. The present study corroborates this conclusion for the human subject as well.

Propylene used as a general anesthetic in man produces complete anesthesia after an average of eight inhalations. There occurs no struggling or any reactive symptoms during the period of induction. During complete anesthesia the breathing is quiet and regular. The heart remained uninfluenced by the anesthetic except for a diminution of sinus arrhythmia during complete narcosis. The pulse rate and the character of the pulse as well as the electrocardiogram remained unchanged. Recovery from the anesthetic was prompt in each instance, with remarkably immediate return of memory, the patient promptly pressing his hand signal, believing that he was "still going under" after even ten minutes of complete anesthesia.

The quicker induction resulted when the mixture contained 50 per cent of propylene.

REFERENCES

- ¹RIGGS, L. K. Anesthetic properties of the olefine hydrocarbons, ethylene, propylene, butylene and amylene, Jr. Am Pharm Assoc, 1925, xiv, 380-387.
- ²RIGGS, L. K.: The physiologic properties of some unsaturated hydrocarbons, Proc. Soc. Exper. Biol and Med, 1924-25, xxii, 269-270.
- ³RIGGS, L. K., and GOULDEN, H. D. Studies of physiological action of propylene, Anesth and Analg, 1925, iv, 299-307.
- ⁴HALSEY, J. T., REYNOLDS, C., and COOK, H. B.: Some observations on a new anesthetic gas, New Orleans Med and Surg Jr, 1924-25, lxxvii, 29-30.
- ⁵HALSEY, J. T.; REYNOLDS, C., and PROUT, W. A.: Anesthetic properties of propylene, Anesth. and Analg, 1925, iv, 195-198.
- ⁶HALSEY, J. T., REYNOLDS, C., and PROUT, W. A. A study of narcotic action of propylene, Jr. Pharmacol and Exper Therap, 1925-26, xxvi, 479-490.
- ⁷BROWN, W. E. Experiments with anesthetic gases, propylene, methane, dimethyl-ether, Jr. Pharmacol and Exper Therap, 1924-25, xxiii-xxiv, 485-496.
- ⁸CAINE, A. M., and REYNOLDS, C. Electrocardiographic studies of the action of propylene, and some other anesthetic gases, Proc Soc Exper Biol and Med, 1925-26, xxiii, 488.
- ⁹REYNOLDS, C. Comparative studies of propylene, ethylene, nitrous oxide and ether, Jr. Pharmacol and Exper Therap, 1926-27, xxvi-xxvii, 93-99.

Editorials

HEREDITY OF ELLIPTICAL ERYTHROCYTES (OVALOCYTOSIS)

An interesting sequel has appeared to a study which was published in the *ANNALS* in 1929 of a family showing elliptical erythrocytes. In this paper by Hunter and Adams¹ personal observations were reported of three generations of a family of Dutch extraction, one member of which was living in Portland, Oregon, and the others near Missoula, Mont. Twelve members of this family were found to exhibit the anomaly in question, consisting of the presence in the circulating blood of elliptical, elongated and irregularly shaped erythrocytes. Differences were recognized and established between this condition and the more common sickle cell anemia. Several members of the family were more or less anemic and one showed a marked anemia, which improved under liver therapy. The twelve individuals showing the anomaly were members of three generations: a grandfather, each of his eight children, five boys and three girls, and three of six grandchildren, a boy and two girls, who were children of two daughters in the second generation. Prior to the emigration of the grandparents to this country none of the family, as far as known, had ever been outside the boundaries of Holland. For generations, the men were farmers and lived in the village of Zevenhuisen near

Amsterdam. This paper attracted the attention of Professor A. A. Hymans van den Bergh of the University of Utrecht, not only because it added a considerable number of new cases of this anomaly in which he was already interested, but also because the family was of Dutch extraction. He accordingly obtained the family name from the American authors and through a member of his staff investigated the branches of the family still resident in Holland. The results of this search have now been published.² Although the investigation was rendered difficult and in part incomplete because of the dispersion of the family and the refusal of certain of the parents to permit examination of their children, four additional examples of the anomaly were discovered. It was learned that the branch of the family in America had originated from the third marriage of the great grandfather, who had been married four times. From the first marriage there was no issue. Among the descendants in the lines resulting from the second and fourth marriages there was not a single example of elliptical erythrocytes.

¹HUNTER, WARREN C. and ADAMS, RICHARD B. Hematologic study of three generations of a white family showing elliptical erythrocytes, *Ann Int Med*, 1929, 11: 1162-1174.

²VAN DEN BERGH, A. A. HYMANS. A propos des hématies elliptiques (l'ovalocytose), *Rev Belge d Sci Med* 1931, 11: 683-688.

It therefore was evident that the anomaly had been introduced by the third wife. Accordingly, the investigation was broadened to include her collateral lines. It was found that she was one of seven children, all deceased, but only certain of the children of one of her sisters could be examined. In this family of eight children, three of the five examined were found to have elliptical red blood cells. A daughter of one of these made the fourth example in this line, and the sixteenth in the combined group. It is unfortunate that the numerous other collateral lines could not be investigated. From the combined genealogical charts of Hunter and Adams and of van den Bergh, it is shown that in this family the condition of having elliptical erythrocytes is inherited as a dominant trait, appearing only in the offspring of affected individuals and is transmissible by either sex. This affords another striking example of the inheritance of a hematic condition.

SIGNIFICANCE OF POSITIVE ASCHHEIM-ZONDEK TEST IN THE MALE

The biological relationship between host cells and tumor cells in patients with malignant teratomas of the testis containing chorionic epithelial structures is unlike that which can occur in the male under any other circumstances. If the included blastomere theory of the origin of complex teratomas of this type is accepted, it means for the male that in his testis there is growing a structure composed in part of the fetal components of the placenta belonging to his included twin brother. The adult male body is thus subjected

to hormonal influences normally experienced only by the female. That significant hormonal activity attaches to this neoplasm has been known for a good many years. Enlargement of the breasts is an extremely common finding with testicular chorio-epithelioma (malignant syncytioma), so that the examining physician has utterly failed in his duty to his patient if he does not make a careful examination of the testes when confronted by gynecomastia. If no intrascrotal tumor is found, but one testis is undescended, the cryptorchid is under a special burden of suspicion. If histological examination of the breast is possible, it will be found that the gynecomastia is of the type of a functional hypertrophy rather than the excessive fattiness of the enlarged breasts of pituitary dystrophy. There is clinical evidence of a quantitative relationship between the amount of living chorio-epithelial neoplasm and the degree of hormonal activity. In an instance known to the writer a surgeon removed a male breast showing marked enlargement due to functional hypertrophy. At the suggestion of a pathologist he enlarged his field of physical examination and found a testicular neoplasm which, when removed, proved to be in part chorio-epitheliomatous. The remaining breast, which was enlarged, but to a less marked degree than the one removed, decreased to about normal size before the patient left the hospital. However, when he returned a number of months later with innumerable metastases, all of which showed the usual mélange of syncytial cells and those from the Langhans' layer, the remaining breast

had reached a size larger than that of the other at the time it was amputated. This constituted an unintentional, but none the less controlled, biological experiment.

Further evidence of the hormonal aspect of this neoplasm rests on the occasional observation that after the removal of a primary chorio-epithelioma, its secondaries may undergo spontaneous retrogression. Unfortunately, this is apparently a rare occurrence which is limited to the less malignant forms and has been described only for the similar tumor in the female following pregnancy, in which the genetic relationship between host cells and neoplasm cells is more remote.

It is not surprising, in view of these clinical evidences, that a biologic means of detecting this hormone should be found in the Aschheim-Zondek reaction for the recognition of the presence of Prolan A. A summary of the scant earlier data on this subject and considerable new evidence are found in an extremely interesting paper by Ferguson and his associates¹ at the Douglas Research Laboratories of the Memorial Hospital, New York City. The question is complicated by the occurrence of positive reactions in the presence of carcinoma in the female, especially of genital carcinoma. Thus Zondek found forty-five positive reactions among fifty-five cases of genital carcinoma in non-pregnant women, and five positive reactions in a

group of fourteen women with extragenital carcinoma. At the time when Ferguson's paper was written Zondek had reported upon a group of men with extragenital carcinoma, thirty in all, of whom four gave positive reactions, and upon a group of four men with genital carcinoma, of whom two with carcinoma of the prostate gave negative reactions and two with neoplasms of the testis, not verified histologically, gave positive reactions. Heidrich and Fels had found a positive reaction in a man, thirty-five years old, with a proved chorio-epithelioma of the testis. Ferguson and his group found negative reactions in fifteen men with normal testes, including three who were normal and twelve with extratesticular carcinoma. Negative reactions were found also in twenty-four with non-malignant lesions of the testes, only one of which was a blastoma. Eight cases with testicular teratoma all gave positive reactions. Of four cases of teratoma without clinical evidence of disease for three months to three years, three had negative reactions and the fourth who had had the right testis removed ten years before under a diagnosis of sarcoma and the right testis removed three months before for a proved embryonal carcinoma, gave a positive reaction. The suggestion is made by the authors that a lack of balance of the hormone of the anterior hypophysis due to his castrate condition might explain the positive reaction of this castrated, but certainly insufficient time had elapsed to eliminate the possibility of subclinical metastasis. From the results reported, it would seem that the Aschheim-Zondek reaction provides a re-

¹FERGUSON, RUSSELL S., DOWNES, HELEN R., ELLIS, EDWARD, and NICHOLSON, MARY E. Preliminary note on a new method of differentiating the testicular tumors by biological means, *Am J of Cancer*, 1931, **xv**, 835-843.

markably consistent method of determining the presence of malignant tumors of the testis at an early date (43 days from the known date of onset in one instance) in the course of the disease. The importance of this in differential diagnosis and in the presence of cryptorchidism can readily be appreciated. From the results available this reaction does not appear to differentiate chorio-epithelioma from other forms of malignant teratoma of the testis. It would require serial sections of the entire growth, however, to rule out beyond any doubt, the possibility that malignant syncytioma was present. It is probably that most, if not all, testicular teratomas are originally trigeriminal and that one or more cell types, acquiring the attributes of malignancy, outgrow all of the others.

A still broader significance may at-

tach to this line of investigation. Normal chorionic syncytium and cancer cells have much in common: extraordinary reproductive energy, rapidity of growth, invasive power coupled with destruction of the recipient tissue, and striking facility for hematogenous dissemination. When chorionic syncytial giant cells lodge in the lung, as they do with every childbirth, they soon die; but when carcinoma cell emboli lodge in the lung, they survive and grow only too frequently. One succumbs, apparently, to an anti-syncytial hormone; against the other no such defensive mechanism seems to be at hand. The Aschheim-Zondek reaction, or modifications of the same principle, may eventually give much information about the biologic relationship of the cancer cell to its host tissue, as it affects the hormonal balance of the entire organism.

Abstracts

The Diagnostic Program in Food Allergy
By WARREN T. VAUGHAN, M.D. (Am Jr Med Sci, 1931, clxxxii, 459-467)

From the past history, and the family history, the probability of the existence of an allergic state can usually be determined, and the history of each attack may, if carefully gone into, furnish good clues to foods which should be suspected. Thorough physical examination and careful laboratory investigation must be utilized in order to recognize such associated organic diseases as may be present. Both the scratch method and the intradermal technic have a distinct place. The latter is much the more sensitive but should not be done without preliminary scratch studies. If the skin tests are negative or if, after trial, it is learned that all of the allergenic foods have not been discovered, two other methods of study remain. If the symptoms manifest themselves at intervals of several days, the *food diary* in which the patient tabulates all substances which he ingests and notes the appearance of allergic manifestations may reveal the offending substances. If the symptoms are fairly constant or appear at frequent intervals, the *trial diet* may be of the greatest value. In this connection the author emphasizes the importance of giving due regard to the biological grouping of food substances. When one member of a botanical food group has been proven allergenic to an individual, other members of the same group may cause allergic symptoms, even though their skin test reactions have been negative. Sometimes a positively reacting member of a group is found to give rise to no symptoms whatsoever, while a negatively reacting member of the same group does cause trouble. However, if one is sensitive to one member of a group, it does not necessarily follow that all other members will produce symptoms. On the background of these various considerations, a basic list of foods for use in the formulation of the trial diet

is proposed. Any such diet must be followed rigorously for at least two weeks before one can be certain of the results.

I Anemia of Dogs Produced by Feeding of the Whole Onions and of Onion Fractions II Anemia in Dogs Produced by Feeding Disulphide Compounds By O. M. GRUBER, M.D., (Am Jr Med Sci, 1931, clxxxii, 812-815, 815-820)

The feeding of raw or autoclaved onions or their juice to adult dogs resulted in a severe anemia, confirming the findings of Sebrell in this respect. The animals were fed both the raw and the autoclaved onions in daily doses of 15 gm per kilogram of body weight, and the onion juice in equivalent amounts of 10 cc per kilogram. Uniform results were obtained from the three forms of feeding. Severe reduction in the number of red cells and in the hemoglobin occurred on the seventh or eighth day, when six feedings of onion had been given. There was a simultaneous increase in the white cell count. Hemolysis must play an important part in the red cell destruction for the blood serum became red with hemoglobin. In every case, following the maximum red cell destruction, the animal developed tolerance to onion in any of the three forms administered so that further feeding had no effect on the blood elements. The feeding of the steam distillate of fresh onions and of the residue from the distillation of onions caused little or no change in the blood of dogs, although the distillate possessed an extremely strong odor of onions, and dried onion juice was less effective than the juice itself. It was believed that the active agent in producing the observed effects was probably oil or onions of which allyl propyl disulphide is the chief constituent. Since this compound was not available, closely related substances containing the disulphide linkage were tried. It was found that n-propyl disulphide and di-p-tolyl disulphide caused

severe anemia in dogs through a hemolytic action upon the red cells. The rapid hemolysis was followed by a high degree of leukocytosis and marked signs of red cell regeneration. The benzyl disulphide, although isomeric with the di-p-tolyl disulphide, lacks entirely the hemolytic action of the latter. Repetition of a course of treatment with n-propyl disulphide showed no evidence of the acquisition of tolerance such as followed onion feeding.

Autopsy Observations on One Hundred and Sixteen Cases of Malignant Disease, in Eighty-Nine of Which Experimental Injections of Suprarenal Cortex (Coffey-Humber) Were Given By HOWARD A. BALL, M.D., (Am. Jr. of Cancer, 1931, xv, 1352-1360)

The 116 cases of malignant disease used in this study were divided into three groups, a *basic control series* composed of 25 cases of malignant disease, previously examined post-mortem by the author, in which application had been made for extract injection, but in which death had occurred before any extract was administered, a *relative control series* consisting of 47 cases receiving from 1 to 15 injections, or not more than 105 cc of the experimental adrenal cortex extract, and an *experimental observation series* consisting of 42 cases in which more than 15 injections, or more than 105 cc of the extract, had been given. Since necrosis and sloughing were the chief anatomical changes claimed by Coffey and Humber in their patent application, these manifestations were watched for especially. Necrosis and sloughing were observed frequently and occasionally seemed to be of greater degree or further extent than one would be led to expect from observation of similar uninjected cases. They occurred, however, without correlation to the total amount of extract injected and the difference in these respects among the three series was too slight to be significant. Likewise no essential difference in the incidence of necrobiosis was found on microscopical examination, using nuclear fragmentation and "replacement fibrosis" as criteria. In 28 per cent of the 89 cases which had received the extract, metastases were found in the adrenals. No essential change from the

usually observed characteristics of malignant tissue in far advanced cases could be determined in the two series that received the experimental suprarenal cortex extract (Coffey-Humber), and there were no significant differences between the series that had received less than 15 injections and that which had received more than that amount of treatment.

Extensive Atrophy of Subcutaneous Fat Following the Repeated Injections of Insulin By JOHN R. WILLIAMS, M.D., F.A.C.P. (Jr. Lab and Clin. Med., 1931, xvi, 1911-1197)

That it is important for the patient self-administering insulin to vary the site of the injection, and equally important for the physician to make occasional physical inspections of the regions used, is shown by the increasing group of cases in which local atrophy of the subcutaneous fat occurs. The author reports and illustrates such a case. A woman, aged forty-four years, who had been taking two doses of insulin daily for nearly three years remarked upon the hollows in her thighs. Examination revealed a marked atrophy of the subcutaneous fat on the anterior surfaces of both thighs. The atrophic areas were irregular in shape and from 8 to 15 cms in diameter with the longer axis parallel to that of the thigh. These cavities were from 2 to 3 cms deep and gave the impression that the fat had been completely excavated from beneath the skin of the involved areas, for the muscles and blood vessels beneath could be distinctly felt. There was no evidence of soreness or inflammation. Similar changes were noticed in a girl who was taking four small doses of insulin daily. In this case, after avoiding injection of the areas of atrophy for some time the defects disappeared, apparently being filled in by new fat. The cause of this unusual atrophy is unknown, but a low grade inflammation with fibrosis may be the important factor.

Provisional Birth, Death, and Infant Mortality Figures, Birth Registration Area, 1930 (Public Health Reports, 1931, xlv, 2373-2376)

The Department of Commerce, through the Bureau of the Census, Division of Vital

Statistics, announces that in 1930 in the birth registration area (exclusive of Utah) there were reported 2,190,047 live births. This is an increase of 15 per cent over the number reported from the same area in 1929. Birth rates were higher in 26 states in 1930 than in 1929. In both years New Mexico has had the highest birth rate of any state, while Oregon has had the lowest rate in each of the two years under comparison. In the birth registration area (exclusive of Utah) the death rate in 1930 was 11.3. This is 0.6 lower than for 1929. The infant mortality rate for 1930 was 64.2, the lowest since the establishment of the birth registration area in 1915. In thirty-seven states an infant mortality rate was attained lower than that of the preceding year.

Carcinoma of the Stomach in a Negro of Twenty-Four Years By JAIME DE LA GUARDIA. United Fruit Company, Medical Department, Nineteenth Annual Report, 1930, 144-148.

The occurrence of an advanced scirrhous carcinoma of the stomach in a Haitian negro 24 years of age is of interest from the standpoints both of age incidence and race incidence. The history revealed the onset of the condition to have antedated his entrance into the hospital and subsequent diagnosis by at least two years. A wide resection of the stomach was done with gratifying immediate post-operative results. The patient died about four months later of recurrence and generalized carcinomatosis.

Reviews

The Renal Lesion in Bright's Disease By THOMAS ADDIS, Professor of Medicine, Stanford University, and JEAN OLIVER, Professor of Pathology, Long Island College of Medicine, Formerly Professor of Pathology, Stanford University. xi + 628 pages, 170 full page plates, 2 in color, 21 text illustrations and 1 folding table. Paul B. Hoeber, Inc., New York City, 1931.

One need not go far into this book by Addis and Oliver to realize that he has before him a work which is unusual in its straightforward objectivity. It is easy to prophesy for it an influence which may pervade medicine for a long time to come. It does more than set forth that which its title foreshadows, it points the way to a method. As did Bright in 1827 and Volhard and Fahr in 1914, the authors develop a comparison of clinical and pathological facts in order to determine the degree of correlation between them. Hence the method must be objective and it must be characterized by strict intellectual honesty. That such is the case there is abundant evidence throughout the work. Clinical methods and definitions in connection with the renal lesions of Bright's disease are first

set forth, with a consideration of normality in the characteristics of the urine. More than one practitioner will be surprised to learn that the average rate of cast excretion in 74 supposedly normal medical students was 1040 per twelve hours. The pathological methods of qualitative and quantitative investigation of the renal lesions are also presented with carefully considered definitions of the terms used. The detailed clinical and pathological observations of the 72 cases used in the investigation occupy the next 350 pages. Each case is illustrated by two photomicrographs, one a low power view for general topography, the other of sufficiently high magnification to show the simpler cellular detail and especially valuable because of the wide area utilized, averaging four glomeruli to the field. The clinical and pathological observations are then correlated and a theoretical description of the course and sequence of the pathological processes developed. From this analysis a classification of Bright's disease satisfactory to both clinician and pathologist is proposed. The authors recognize as the main group hemorrhagic Bright's disease with initial latent, active and terminal stages, diabetic

erative Bright's disease, and *arteriosclerotic* Bright's disease. In both content and format this book is highly to be commended. One cannot but admire the courage of the publisher who dares to illustrate so profusely, for the illustrations of this book constitute an atlas of the pathology of nephritis. To both clinician and pathologist this work will be of very great value.

Gould's Medical Dictionary. By GEORGE M. GOULD, A.M., M.D., Edited by R. J. E. SCOTT, M.A., B.C.L., M.D. Third edition, revised and enlarged, with illustrations and 173 tables. 1538 pages. P. Blakiston's Son and Company, Philadelphia, 1931. Price, in rigid fabrikoid with thumb index, \$7.50, in flexible binding, plain, \$7.00, with thumb index, \$7.50.

This new edition of Gould's Medical Dictionary requires no introduction, for more than 800,000 copies of its predecessors in their various forms have been sold. When the "Pocket Medical Dictionary" came out in 1892 it contained 12,000 defined words. The edition immediately preceding the one now under review contained over 83,000 words and to that compilation many new terms have been added in the present revision. Certain omissions in the preceding edition, to which attention was called in a review in the *ANNALS* at that time, have been remedied, although it is not clear why 'blastophthoria', thus introduced, is capitalized. Preference is now given to the retention of the final *e* in that series of chemical terms from which it was dropped a number of years ago on the recommendation of the American Association for the Advancement of Science. This is in accord with present day orthography. The inclusion of an enormous store of useful information in tabular form has been an important feature in this series. Among the 173 tables in this edition there are a number of new tables of bacteria, metazoa and pathogenic protozoa, also the International Table of the Causes of Death. In the table of micro-organisms the original names are conveniently arranged in parallel columns with those of the new classification. These

tables are made useful to the great majority of physicians whose bacteriology was not that of the last few years by basing the alphabetical arrangement on the old names which are so much more familiar. Numerous illustrations add greatly to the value of descriptive definitions and those which differentiate between closely similar structures. A medical dictionary should be the most used text of both medical student and practitioner, and this new Gould will be found eminently satisfactory in every particular.

Recent Advances in Radiology. By PETER KERLEY, M.B., B.Ch. (N.U.I.), D.M.R.E. (Camb.), Assistant Radiologist, Westminster Hospital, Radiologist, The Royal Hospital for Diseases of the Chest viii + 324 pages, 120 illustrations. P. Blakiston's Son and Company, Philadelphia, 1931. Price, \$3.50, net.

The significant advances in the physical aspect of radiology, both technical and structural, are largely omitted from this book, for its purpose is to set before the general practitioner, the internist, and the surgeon, that which each must know about the present state of the subject in its clinical applications. Each must know the constantly expanding field of applicability of radiological methods of investigation, their limitations and the underlying principles in the interpretation of radiographs. This means that throughout the book the method of approach is that of correlation of the pathological changes with the radiological appearances. The present state of x-ray therapy is presented in a much compressed final chapter. Not all will agree that "the radiation treatment of malignant disease has now passed through the troublesome optimistic and pessimistic periods, and is established on a scientific basis." However, this chapter is largely free from unjustified enthusiasm for methods of treatment for specific neoplastic conditions and presents those conflicting views which show that the question is still unsettled. One of the most valuable of the many excellent features of the book is the emphasis placed upon what constitutes a suitable film for a particular purpose. Under lung, for instance, are sum-

marized the results of investigations carried on in the Royal Chest Hospital during the last five years. It was found that early tuberculosis is best seen in a film which shows the subclavian arteries, the inferior vena cava, and the normal interlobar pleura between the right upper and middle lobes. The demonstration of these three shadows or, at least, of the vascular ones, was then decided upon as an essential criterion of a suitable film. This text is a worthy addition to the Recent Advances series.

Textbook of Histology for Medical and Dental Students. By EUGENE C. PIETTE, M.D., Pathologist and Director of the Laboratory of the West Suburban Hospital, Oak Park, Illinois, Consulting Pathologist of the Chicago State Hospital, Chicago, Illinois, etc. xvi + 466 pages, 277 illustrations. F. A. Davis Company, Philadelphia, 1931. Price, \$4.50, net.

We are told in the preface of this textbook of histology, intended primarily for medical and dental students, that an author must be first of all a censor, suppressing and omitting anything incomplete and doubtful. There are a number of assertions admitted here, however, which might well have been subjected to a more rigorous censorship. For instance, the statement is made that the hearts of human cadavers have been revived *several days after death* by injecting warm Ringer's solution with glucose into the coronary arteries, such hearts resuming contractions and continuing vital specific activity. Technical methods are briefly surveyed in fifteen pages in which paraffin sections are described as being cut with the knife perpendicular to the long dimension of the piece of tissue, apparently serial sections alone being considered. The celloidin sheet methods for handling paraffin sections are not mentioned. Crenated erythrocytes are said to be of the shape of thorn apples, missing the point that the thorns of the thorn apple (by which hawthorn rather than *Datura stramonium* is usually understood in this country) are not on the fruit. Various other assertions cannot be passed by without a challenge. There is far from general acceptance of the statement that there

are no hemolymph nodes in man, and what reason is there for considering the intrafusal fibers of the muscle spindle as *immature* muscle fibers? Many subjects receive inadequate treatment to meet the needs of the medical students. The palatine tonsil is disposed of in six lines, while the teeth, in probable anticipation of use of the book in schools of dentistry, are granted thirty pages. This book is very well printed and the illustrations, of which none are original, are well reproduced. In view of the effort which has gone into its production, it is a matter for regret that the text does not meet more fully the needs of the student and of the hospital pathologist.

Streptococcic Blood Stream Infections. By GEORGE E. ROCKWELL, M.A., M.D., Associate Professor of Bacteriology, College of Medicine, University of Cincinnati, Member of Senior Medical Staff, Bethesda Hospital, Assistant Director of Bacteriological Service, General Hospital of Cincinnati. ix + 73 pages. The MacMillan Company, New York City. 1931. Price \$1.75.

This short monograph discusses streptococcic blood stream infections under eight chapter headings: Infection, Resistance, the Streptococci, the Patient, the Diagnosis, the Blood Culture and the Treatment. The presentation of this material is far from exhaustive, the content not exceeding that which might be reasonably required of a medical student. There are frequent misspellings of such ordinary terms as 'aldehyde', 'tonsillitis', and 'cholecystitis', and marked inconsistency in orthographic style. Words of the series having the root 'αιμα' at the beginning, such as *hemolysis* are spelled with the diphthong, while the single vowel is used in all forms having the same root at the end of the word, such as *septicemia*. The omission of *endocarditis viridans* and *scarlatina* from the index reveals the level of content. The chapter on treatment is the best part of the book. Here the author writes vigorously and convincingly in evaluating the various therapeutic measures which have been proposed.

College News Notes

PROPOSAL OF NEW MEMBERS

The attention of all Masters and Fellows of the College is called to the By-Laws, Article V, Section 3 (c), Paragraph 2

"After 1931, a candidate for Fellowship shall be eligible only if already an Associate, except upon recommendation of the Committee on Credentials, by reason of very special qualifications"

Masters and Fellows who have candidates to propose for Fellowship should see that the forms are executed and filed in the office of the Executive Secretary of the College before December 31, 1931

Attention is also called to the "Introductory Statement" appearing in the 1931-32 Directory of the College, especially paragraph 1 on page 22. Those Associates who have been elected since April 1, 1929, according to the By-Laws, must qualify for Fellowship within a period of from three to five years from the time of their election. Article VI, Section 3, of the By-Laws, provides that at the expiration of three years, an Associate shall be notified in writing of his eligibility for advancement to Fellowship during the next two years, providing he shall meet within that time the requirements necessary for Fellowship. If not elected to Fellowship within five years, his Associateship will automatically cease. In accordance with the above provisions, Associates eligible for proposal to Fellowship at the next Clinical Session have been notified.

Proposals for Fellowship now on file will be acted upon at a late autumn meeting of the Board of Regents. Proposals for Associateship will be acted upon during the San Francisco Clinical Session, due to the fact that they must first be approved by the Board of Governors before election by the Board of Regents. All proposals must be filed thirty days in advance of action.

1931-32 DIRECTORY

The Executive Secretary of the College completed the publication of a new directory of the Masters, Fellows and Associates during the past summer, and distributed a copy to all members in good standing on September 20. Although the contents have been limited to the most important biographical data, the volume has grown to one of four hundred and thirty-three pages, the compilation of which was a considerable task. Some members failed to return the biographical data sheets, in which cases their previous data were published. However, the great majority co-operated promptly, and a directory to a high degree inclusive and up to date has been produced. Members are requested to advise the Executive Secretary of any misprints, incomplete or imperfect data, so that corrections may be made in the next issue. This directory has become an important reference and guide for physicians and institutions all over the country.

Any member of the College in good standing who by any chance failed to receive the above mentioned directory during September is requested to communicate with the Executive Offices of the College. It has been determined that some copies were held at the Canadian Customs Office and not delivered. In a few other instances, copies may have failed to reach their destinations due to changes of address.

Dr. George E. Pfahler (Fellow), Professor of Radiology, Graduate School of Medicine of the University of Pennsylvania, attended the Third International Congress of Radiology held at the Sorbonne in Paris during the past summer. Dr. Pfahler presented a paper entitled "Roentgen Therapy in Carcinoma of the Breast—A Statistical Study of the Results in Over 1,000 Cases".

At the opening of the Congress, Dr. Pfahler presented an ivory gavel carved from the

tusk of a mastodon, imbedded for probably a million years in the ice of Alaska, to the President of the Congress, Dr Antoine Béclere. In his presentation, Dr Pfahler explained that not all in America is new and young, but that we too have our antiquities

Dr Edward A Strecker (Fellow), Philadelphia, has been appointed Professor of Psychiatry in the University of Pennsylvania School of Medicine

Among recent appointments in the Graduate School of Medicine of the University of Pennsylvania are the following

Dr Ralph Pemberton (Fellow), Professor of Medicine,

Dr William D Stroud (Fellow), Professor of Cardiology,

Dr Truman G Schnabel (Fellow), Assistant Professor of Medicine

Dr Carl V Vischer (Fellow), Philadelphia, is the author of an article entitled "Student Instruction in the Medical Outpatient Department of Hahnemann Hospital of Philadelphia", which appeared in the September number of the Hahnemannian Monthly

Dr G Harlan Wells (Fellow), Philadelphia, is the author of an article entitled "Care of the Heart in the Pneumonia Patient", which was published in the September number of the Hahnemannian Monthly

Dr Ralph Bernstein (Fellow), Philadelphia, discussed the Dermatologic Toxemias of Pregnancy in a contributed article which appeared in a recent issue of the Hahnemannian Monthly

Dr William B Porter (Fellow) Professor of Medicine at the Medical College of Virginia, and Dr Albert H Hoge (Fellow), President-Elect of the West Virginia State Medical Association, were speakers at an alumni meeting of the Medical College of Virginia held at Charleston, October 12. Dr Walter E Vest (Fellow), Huntington, was Chairman of the Committee

Dr Porter and Dr Hoge both addressed the Kanawha County Medical Society at Charleston, October 12

Dr Hoge addressed the West Virginia State Hospital Association at Huntington, September 21, and was also Toastmaster at their annual banquet

Dr Vest was elected President of the West Virginia State Hospital Association, September 21

Dr Henry M Moses (Fellow), Brooklyn, N Y, has been appointed Professor of Clinical Medicine at the Long Island College of Medicine

On October 7, Dr Moses presented a paper on "The Clinical Findings and Methods Used in the Diagnosis of Pulmonary Neoplasms" in a symposium on this subject at the staff meeting of the South Nassau Communities Hospital, Rockville Centre, New York

Dr John V Barrow (Fellow), Los Angeles, lectured before the Hollywood Academy of Medicine, September 24, his subject being "Pathology and Treatment of Amebiasis, with Motion Picture Demonstrations of Organisms and Lesions"

D R Manning Clarke (Fellow), Los Angeles, has been elected Secretary of the Medical Section, California State Medical Association, for the year 1931-32. The next annual session will be held in Pasadena

D Samuel Ayers, Jr (Fellow), Los Angeles, is co-author with Nelson P Anderson and Esther M Youngblood of an article entitled "Fumigation as an Aid in the Control of Superficial Fungus Infections" in the Archives of Dermatology and Syphilology, August, 1931

Dr Ayres is also co-author with Dr Anderson of an article entitled "Dermatitis Medicamentosa Due to Ephedrine" appearing in the August 15, 1931, issue of the Journal of the American Medical Association

Dr G R Maxwell (Fellow), Martinsburg, W Va, has been elected Chair-

Staff of the Monongalia County Hospital Morgantown, for the year 1931-32

Doctors Simon R Blatters, Frank B Cross, Henry M Moses and Philip I Nash (Fellows) have been appointed Professors of Clinical Medicine, and Doctors Murray B Gordon and Paul L Parrish (Fellows) have been appointed Professors of Clinical Pediatrics, at the Long Island College of Medicine. These appointments carry with them seats in the administrative faculty

Doctors E G Thompson, W C Colbert C H Sanford and A F Cooper (Fellows) have recently been advanced to Associate Professors of Medicine at the University of Tennessee College of Medicine Memphis

Dr B M Allen (Fellow), Wilmington Del, addressed the 142nd annual session of the Medical Society of Delaware, October 14, on "X-Ray Diagnosis of the Chest with Special Reference to Fluid"

Dr H O Colomb (Associate), formerly of Providence, R I, has been appointed Clinical Director at the Central State Hospital, Pineville, La., as of October 1, 1931

Dr Solomon L Cherry (Fellow), Clarksburg, W Va, discussed a paper on "Dental Foci of Infection and their Systemic Effects" at a joint meeting of the Harrison County Medical and Dental Societies on October 1

Dr E J Engberg (Fellow), St Paul, Minn, is the author of an article in Minnesota Medicine for October entitled, "Polymyositis in Minnesota"

Secretary Ray Lynian Wilbur who is President of Better Homes in America, has recently appointed Dr James M Anders (Master) Chairman of the Better Homes Committee of Philadelphia for 1932. Dr Anders has also been reappointed a member of the Board of Health of Philadelphia by the present Director of Public Health, Dr Orlando H Petty (Fellow)

At a Clinical Conference held under the auspices of the Staffs of the Leo N Levi Memorial Hospital and Charles Stenberg Clinic, both of Hot Springs National Park, Ark, October 1, 1931, the following Fellows of the College took part

Dr A G Sullivan—"Etiological, Anatomical and Physiological Factors in Heart Disease",

Dr D C Lee—"Laboratory Diagnosis of Syphilis with Demonstration",

Dr Grayson E Tarkington—"Dehydration in Epilepsy",

Dr G B Fletcher—"Types of Paralysis Points in Differential Diagnosis"

Dr Mitchell Bernstein (Fellow), Philadelphia, was elected a member of the Board of Trustees of the Philadelphia College of Pharmacy and Science at its semi-annual meeting, September 28, 1931

Dr J A Myers (Fellow), Minneapolis, has been promoted from Associate Professor to Professor of Preventive Medicine at the University of Minnesota

On September 22, Dr Myers presented a paper before the annual joint meeting of the Medical Society of the County of Queens and the Queensboro Tuberculosis Association, on September 24, a paper before the general session of the 111th annual meeting of the Michigan State Medical Association, on October 2, a paper before the St Joseph, Missouri, Medical Society and the Missouri State Tuberculosis Association, on October 15, a paper before the Illinois State Nurses Association in Chicago, and on November 2, a paper before the Wisconsin Anti-Tuberculosis Association in Milwaukee

Dr William Devitt (Fellow), Founder and Directing Head of Devitt's Camp, Allenwood Pa, on September 18, 1931, was honored by the local Rotary Club of Milton at a dinner and reception given as a means of expressing to the widely known physician the measure of esteem and devotion held for him by his associates in the club, as well as by the thousands of residents of the Susquehanna Valley who have witnessed

his successful efforts at the Sanitarium that bears his name"

Dr Robert G Torrey (Fellow), has been appointed Professor of Principles and Practice of Medicine, succeeding the late Dr L. Napoleon Boston, at the Woman's Medical College of Philadelphia

Dr J M Hutcheson (Fellow), Richmond, Va, and Dr D P Scott (Fellow), Lynchburg, Va, addressed the Mecklenburg County Medical Society, September 15, on "Clinical Aspects of Coronary Thrombosis" and "Treatment of Nervous Patients", respectively

At the Roanoke Meeting of the Medical Society of Virginia, October 6-8, 1931, Dr D C Wilson (Fellow), Professor of Nervous Diseases at the University of Virginia, and Dr Beverley R Tucker (Fellow), Professor of Neurology and Psychiatry at the Medical College of Virginia, were speakers in connection with the mental hygiene symposium

Dr Horton Casparis (Fellow), Professor of Pediatrics at Vanderbilt University, Nashville, as guest speaker before the Virginia Pediatric Society, October 7, used as his title "Tuberculosis in Children Prevention and Control"

Dr A L Gray (Fellow), Richmond, Va, is President of the Virginia Roentgen Ray Club, which held its annual meeting at Roanoke in connection with the state meeting, October 7

Dr John E Gardner (Fellow), Roanoke, Va, spent six weeks during the summer in special electrocardiographic work at the Johns Hopkins Hospital, Baltimore

Dr Beverley R Tucker (Fellow), Richmond, attended the International Congress on Nervous Diseases in Berne, Switzerland, during the past summer

Dr D T McCall (Fellow), Mobile, Ala, recently addressed the Monroe County (Ala) Medical Society

Dr Walter S Leathers (Fellow), Nashville, recently addressed a conference of public health workers of Kentucky, Tennessee and Missouri

Dr Lea A Riely and Dr John E Heatley (Fellows), both of Oklahoma City, Okla, gave addresses at the Osage County Medical Society's meeting on September 28, 1931—their subjects being, "The Clinical Aspects of Gall Bladder Disease" and "X-Ray Diagnosis of Gall Bladder Diseases", respectively

Dr Lewis J Moorman (Fellow), Oklahoma City, Okla, has been elected Dean of the University of Oklahoma School of Medicine

Dr John M Thorne (Fellow), Pittsburgh, addressed the McKeesport (Pa) Academy of Medicine, October 26th, on "The Management of Cardio-Renal-Vascular Diseases"

On the recommendation of the Committee on Reorganization of the Sea View Hospital, Staten Island, New York, June 30, 1931, Doctor Louis Faugeres Bishop (Fellow), has been reappointed Consulting Cardiologist at Sea View Hospital

Dr Samuel E Thompson (Fellow), Kerrville, Texas, has been re-elected President of the Southwest Texas District Medical Society

Dr Joseph McFarland (Fellow), Philadelphia, addressed the annual meeting of the Medical Society of Delaware at Wilmington on "Malignant Diseases of the Breast"

Dr Francis E Seneor (Fellow), Chicago, presented a paper on "Modern Conceptions Concerning the Treatment of Syphilis" before the Peoria City Medical Society, October 6

Dr Carl F Moll (Fellow), Flint Mich, was installed as President of the Michigan State Medical Society at Pontiac, September 24

Dr W Bernard Yegge (Fellow) of Denver addressed the Boulder County (Col) Medical Society, October 8, on "Diagnosis and Treatment of Gastric Ulcer".

Dr Henry F Smyth (Fellow), Philadelphia, discussed "The Toxicity of Methyl Alcohol" before the annual meeting of the American Public Health Association at Montreal, September 7-10, 1931

Dr Carl R Howson (Fellow), Los Angeles, addressed the Fresno County Medical Society, September 1, on the subject "Some Points in the Present-Day Treatment of Tuberculosis", and also the San Bernardino

County Medical Society, October 6, on "The Future of Medicine"

Acknowledgment is made of the following gifts of reprints by members to the College Library

Dr George B Fletcher (Fellow), Hot Springs Nat'l Park, Ark—I reprint,

Dr Gustave P Grabfield (Fellow), Boston, Mass—6 reprints,

Dr Samuel J McClendon (Associate), San Diego, Calif—4 reprints,

Dr Aaron E Parsonnet (Fellow), Newark, N J—2 reprints,

Dr Meldrum K Wylder (Fellow), Albuquerque, N M—I reprint

OBITUARY

DR ROBERT GIBBS DOUGLAS

Dr Robert Gibbs Douglas, Associate, Louisiana, died of malignant hypertension on July 23, 1931, aged 45 years

Dr Douglas was born in De Soto Parish, Louisiana, in 1885. He received his academic education at the University of Louisiana, while his medical degree was obtained from Tulane University of Louisiana School of Medicine in 1919. During 1920 his internship was spent in the City Hospital, St Louis, Missouri. He returned home for a year and associated in practice with Dr L T Baker of Dixie, Louisiana, where he remained until he became associated with the Highland Clinic in 1922. From that time until his death, Dr Douglas confined his work to the study and practice of internal medicine. He en-

deared himself to his associates and to the community in general. At the time of his death he enjoyed a very large practice.

Dr Douglas was a member and ex-President of the Caddo Parish Medical Society and a member of the Southern Medical Association, the Louisiana State Medical Association and the American Medical Association. He was elected to Associateship in the American College of Physicians during 1925.

He was a man of unusual ability, a gifted orator and a most lovable character, generous almost to a fault, never sparing himself in his endeavor to alleviate suffering. The Highland Staff has lost one of its most valuable coworkers and the community one of its most respected citizens.

(Furnished by T P. Lloyd, M D, F A C P, Shreveport, La)

Observations On Pneumococcus Type III Pneumonia*†

By FRANCIS G BLAKE, A B, M D, F A C P, *New Haven, Conn*

DURING the last two decades there has been a gradually but steadily increasing tendency to classify pneumonia on an etiological basis rather than on the older, anatomical basis of Laennec, or at least, if the anatomical terms of lobar and bronchopneumonia are retained, to qualify them by an additional etiological diagnosis. This change which has taken place in the classification of pneumonia has undoubtedly occurred because of the increasing recognition of the fact that pneumonia comprises in reality a considerable group of quite different and distinct infectious diseases hitherto all classified under one or the other of two headings—lobar or bronchopneumonia, primarily on the basis of anatomical considerations, but also in part on symptomatology. Etiological differentiation has been particularly emphasized by Cecil¹, and has been ably discussed by Cole² in his DeLamar Lecture of 1927. In one of his concluding paragraphs Cole says, "acute lobar pneumonia due to pneu-

mococcus type I and acute lobar pneumonia due to pneumococcus type II are specific infectious diseases, just as typhoid fever is a specific infectious disease. The other varieties of acute lobar pneumonia are not such well characterized conditions."

Of these other varieties, pneumococcus type III pneumonia has seemed of particular interest for three reasons: first, because it has a very high case fatality rate of 40 to 50 per cent, secondly, because, although highly fatal, it is caused by a type of pneumococcus which apparently leads a harmless, saprophytic existence in the mouths of a considerable proportion of normal, healthy individuals³; and thirdly, because, in spite of this fairly wide distribution of type III pneumococci and consequent frequent opportunity for infection, the incidence of type III pneumonia is usually recorded as being relatively low when compared with that of pneumonia due to type I and to type II pneumococci, organisms which are not found in the mouths of normal individuals except in rare instances³.

Previous studies by Cecil, Baldwin and Larsen⁴ have suggested that these peculiarities of type III pneumonia may be related to its apparently preponderant incidence in the later decades.

*From the Department of Internal Medicine, Yale University School of Medicine and the Medical Service of the New Haven Hospital.

†Read at the Baltimore Meeting of the American College of Physicians, March 25, 1931.

of life, frequently in individuals who are the subject of chronic disease, and that in reality the type III pneumococcus is not the highly virulent organism for man which the high mortality of type III pneumonia would seem to indicate

In an effort to see whether additional information bearing on the foregoing suggestions might be obtained and also to characterize type III pneumonia more definitely as a specific disease, a detailed study has been made of 122 consecutive cases admitted to

group IV cases have not been analyzed, since they have not been classified into the numerous specific types of varied virulence and prevalence included in the group IV pneumococci.

INCIDENCE

The relative incidence of the type III infections is shown in table I and is comparable to that previously reported by others. Of the 606 cases of pneumococcal pneumonia in the series, 122, or 20 per cent, were type III, while type I and type II infections to-

TABLE I
Relative Incidence of Pneumococcus Type I, II, III and IV
Pneumonias, Jan 1, 1921, to Jan 1, 1931

Type	Number	Per Cent	Died	Per Cent
Type I	194	32	45	23.2
Type II	79	13	32	40.5
Type III	122	20	54	44.3
Group IV*	211	35	54	25.6
Total	606	100	185	30.5

*Atypical IIs included with the Group IV cases

the New Haven Hospital during the ten year period from January 1, 1921, to January 1, 1931. The series includes all type III cases treated on the Medical Service during this period, 104 in number, and 18 cases from the Pediatric Service* admitted since September, 1927, the bacteriological diagnosis of pneumonia on the children's wards not having been carried out before then. For the sake of comparison certain features of the pneumococcus type I and pneumococcus type II pneumonias admitted during the same periods have been studied. The

together numbered 273, or 45 per cent. There were in addition 211 atypical II and group IV cases, or 35 per cent.

The incidence of the type III pneumonias according to age is shown in chart I. This brings out very clearly the relatively high incidence in the later decades of life. In this series 50 per cent of the cases were 55 years of age or older, while only 15.6 per cent occurred between the ages of 10 and 40. By way of contrast it is shown that the type I and type II cases of this series occurred largely in childhood and early adult life, approximately 50 per cent of the type I cases being under 30 years of age; 87 per cent under 50, while of the type II cases 42 per cent

*I am greatly indebted to Dr. J. D. Trask for the privilege of including the cases from the Pediatric Service.

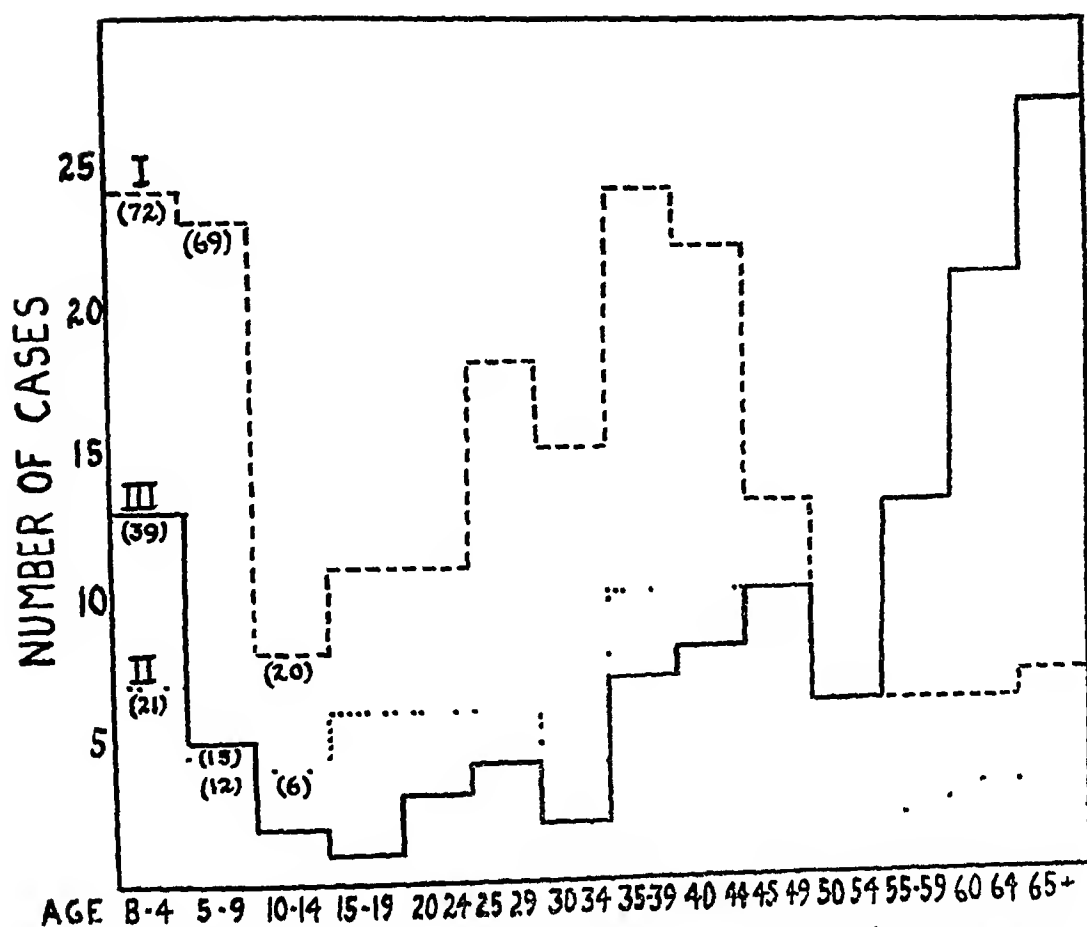


CHART I Incidence of pneumococcus type III pneumonia according to age, pneumococcus type I and pneumococcus type II pneumonia included for comparison

were under 30, 82 per cent under 50. In as much as the cases under 12 years of age occurred during a period of $3\frac{1}{3}$ years and those of 12 years of age or older during a period of 10 years it is obvious that the number of cases in infancy and childhood should be multiplied by 3 in order to approxi-

mate more nearly the actual age distribution. This correction is indicated on chart I by the figures in parentheses. The corrected percentages for the different age periods are shown in table 2.

The relative incidence of type I, II, and III infections at different age

TABLE 2
Percentile Incidence of Type III, Type I and Type II
Pneumonia According to Age

Age	Type III	Type I	Type II
Birth-9	34.2	47.0	32.0
10-39	12.0	33.0	36.9
40-54	15.2	13.7	24.3
55+	38.6	6.3	6.8

periods is brought out more clearly in chart 2 from which it will be seen that approximately 70 per cent of the cases over 60 years of age were type III while only 5 to 17 per cent of those between 10 and 40 years of age were type III cases

The incidence according to sex showed a preponderance of males at all ages, there being 80 cases in males, 42 in females The incidence according to race showed nothing significant, there being 44 Americans of British ancestry, 20 of Irish descent, 14 of the Hebrew race, 12 Italians, 8 Scandinavians, and 5 Germans The remainder were of miscellaneous origin

Incidence and mortality according to months is presented in chart 3 Type III pneumonia does not appear to differ from that due to other types

of pneumococci in its seasonal distribution, the great majority of the cases occurring between October and May, with a very low incidence during the summer In this series the mortality was higher during the fall and early winter than during the spring

PREDISPOSING CAUSES

The rôle of acute predisposing causes immediately preceding the onset of type III pneumonia was very high in this series and apparently played an important part in the etiology of the disease at all ages This is shown in table 3 As would be expected, the acute respiratory infections were outstanding and served as the predisposing cause in 52 per cent of the 115 cases in which information was obtained. Severe exposure, exhaustion and acute

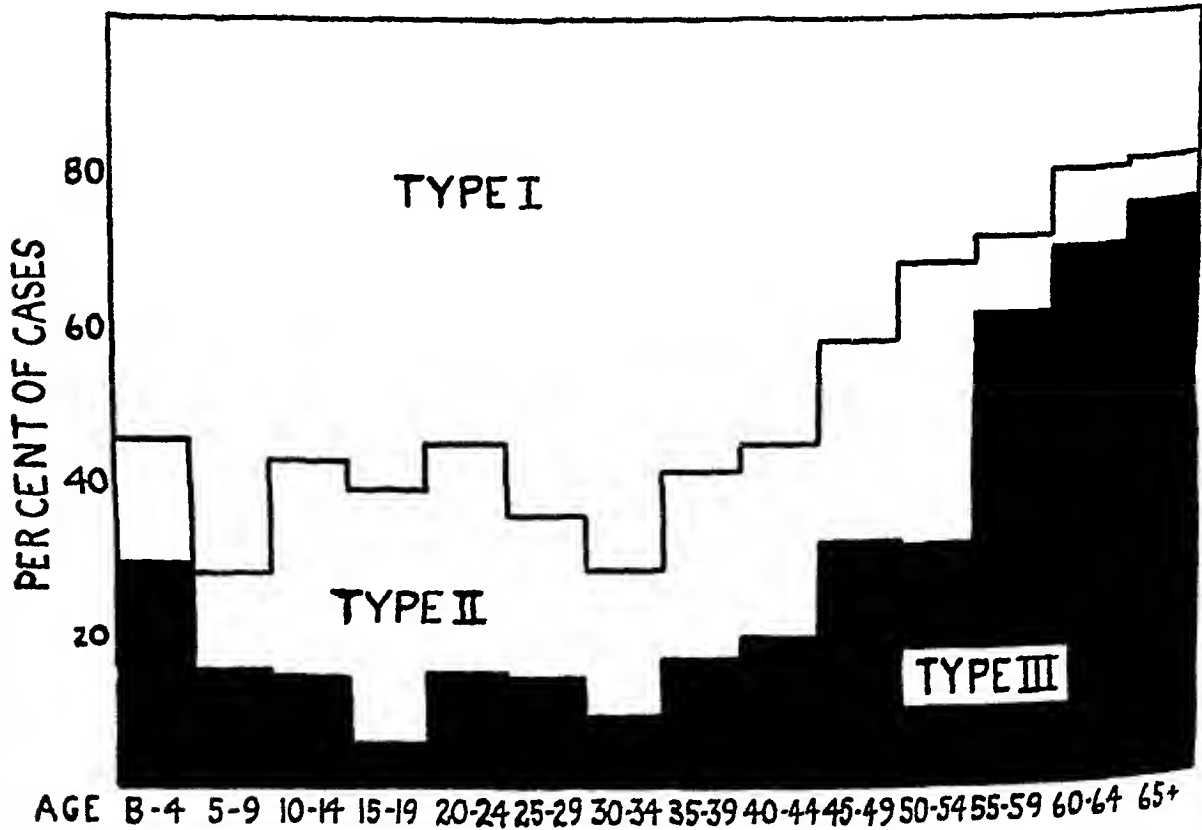


CHART 2 Relative incidence of pneumococcus type I, type II and type III pneumonias according to age

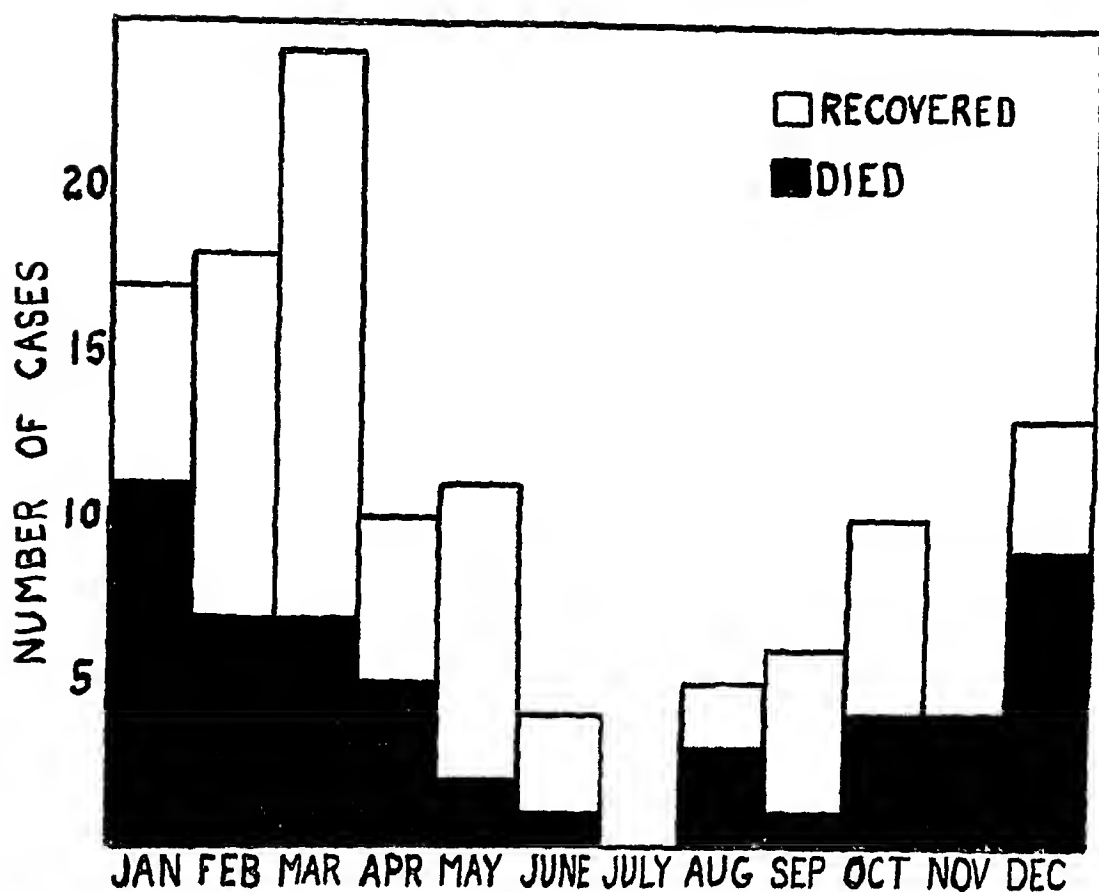


CHART 3 Monthly incidence of pneumococcus type III pneumonia

TABLE 3
Acute Predisposing Causes in Pneumococcus Type III Pneumonia by Decades

	B - 9	10 - 19	20 - 29	30 - 39	40 - 49	50 - 59	60+	Total
Common Cold + Exposure + Alcohol	7		3	3	5	6	19	45
"Grippe" + Exposure + Alcohol				1		1	2	-
Influenza		1	2	2	1	1	1	8
Exposure and Exhaustion					1	2	6	9
Acute Alcoholism					3	1	2	6
Measles	1							1
Pertussis	4							4
Miscellaneous Acute Infections	1	2			3		1	7
Total	13	3	5	7	14	13	22	87
None	5		2	2	2	5	12	28
Undetermined					2	1	4	7

alcoholism also played a considerable part, being recorded as etiological factors in 20 cases. In all an acute predisposing cause was present in 87, or 75 per cent of the 115 cases.

Cecil, Baldwin, and Larsen⁴ called attention to the frequency of chronic diseases in persons who contract type III pneumonia. An analysis of our cases (table 4) amply confirms this. Seventy-nine of the 119 cases in which observations were available, were subject to chronic disease. This might be expected in the patients over 50 years of age, all but 8 of whom suffered from one or more chronic diseases. Of particular interest, however, is the fact that 19 of the 32 patients between 20 and 50 years of age had chronic diseases, 12 with pregnancy are included, and of these, 12 died, while of the 13 in good health only 2 died, one with influenzal and pneumococcus type III pneumonia, the other of a complicating hemolytic streptococcus infection. To what extent chronic disease acts as a predisposing cause is perhaps uncertain, but that it is an important etiological factor there would seem to be little doubt. Particularly significant is the fact that 32 patients in the series suffered from fairly severe, chronic, pulmonary disease, including bronchial asthma, 5, chronic bronchiectasis, 1, chronic bronchitis usually with emphysema 25, and advanced tuberculosis 1. Arteriosclerotic vascular disease, often with heart disease and some degree of heart failure, was present in 39 cases, severe, chronic alcoholism in 11, syphilis in 7, diabetes in 4, and miscellaneous conditions in the remainder. That chronic disease plays an important role in the high

mortality of type III pneumonia seems unquestionable. This relationship will be discussed in a subsequent paragraph.

CLINICAL COURSE

The symptoms of onset and the clinical course of type III pneumonia as exhibited in this series of cases showed no conspicuous differences from those found in the other types and will be presented quite briefly. The onset was sudden in 78 cases, the initial symptom or combination of symptoms being chill in 50, pleural pain in 65, vomiting in 31, and convulsions in 4. In 44 the onset was gradual. There was a definite relation between the method of onset and age in that the onset was much more frequently sudden in patients between 10 and 50 (31), than in young children and those over 50 (151). (Table 5)

The clinical course of the disease presented no unusual characteristics. Sixty-five cases showed pneumonia in one or more lobes of the right lung, of which 34 per cent died, 27 cases showed left-sided involvement, of which 37 per cent died, and 30 cases showed bilateral pneumonia, of which 73 per cent died. (Table 6)

The duration of the disease in uncomplicated cases varied from 1 to 16 days in those that recovered, over 50 per cent having recovered by the eighth day or earlier; from 4 to 12 days in the fatal cases, 50 per cent having died by the sixth day or earlier and 77 per cent by the seventh day. The relation of age to the duration of the disease and the method of recovery in non-fatal, uncomplicated cases is of interest. (Chart 4) In the period of lowest incidence and presumably there-

TABLE 5
Method and Symptoms of Onset in Pneumococcus Type III Pneumonia

Age	Sudden	Gradual	Chill	Pleural Pain	Vomiting	Convulsions
Birth-9	12	7	4	4	8	4
10 - 29	8	2	4	8	3	-
30 - 49	19	7	12	15	9	-
50 - 80	39	28	30	38	11	-
Total	78	44	50	65	31	4

TABLE 6
Extent of Pulmonary Involvement in Pneumococcus Type III Pneumonia

Age	Right		Left		Bilateral	
	Rec	Died	Rec	Died	Rec	Died
Birth-9	9		6		2	1
10 - 19		1	2			
20 - 29	4		1		1	1
30 - 39	3	4				2
40 - 49	8	3	1	2		4
50 - 59	6	4	2		1	6
60 +	13	10	5	8	4	8
Totals	43	22	17	10	8	22
Mortality		34%		37%		73%

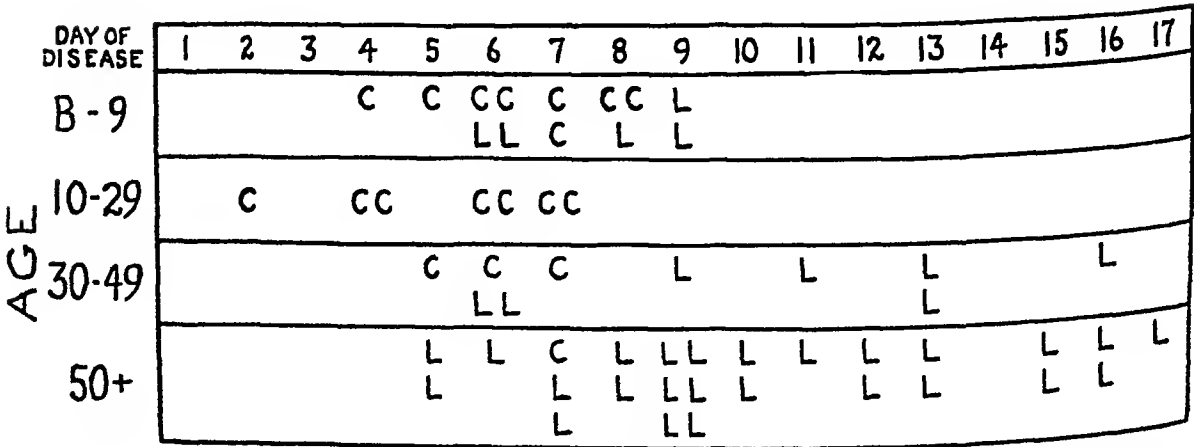


CHART 4 Duration of disease and method of recovery in uncomplicated, non-fatal cases of pneumococcus type III pneumonia C = crisis, L = lysis

fore of greatest resistance, i e, between 10 and 30 years of age, the cases were clinically mild, of relatively short duration and recovered invariably by crisis. In the two periods showing a somewhat higher incidence and presumably greater susceptibility, i e, from birth to 10 years and between 30 and 50 years, the duration was somewhat longer and approximately half of the cases recovered by lysis. In the period of high incidence and relatively high susceptibility after the age of 50, the disease was of still longer duration and recovery by crisis very rarely occurred. In fact, after 60, the average duration in 17 cases was 10 days and no case showed a critical recovery. A

glance at chart 4 will show that one should be very hesitant about predicting an early recovery by crisis in patients over 30 with type III pneumonia.

Three factors bearing directly on the debatable question concerning the virulence of type III pneumococcus for man, namely, the frequency and degree of bacteremia, the frequency and severity of pneumococcus complications, and the mortality, are of special interest.

The frequency of positive blood cultures in this series is shown in chart 5 and is compared with the frequency of bacteremia in the type I and type II pneumonias in the series. In the fatal cases bacteremia was consistently less

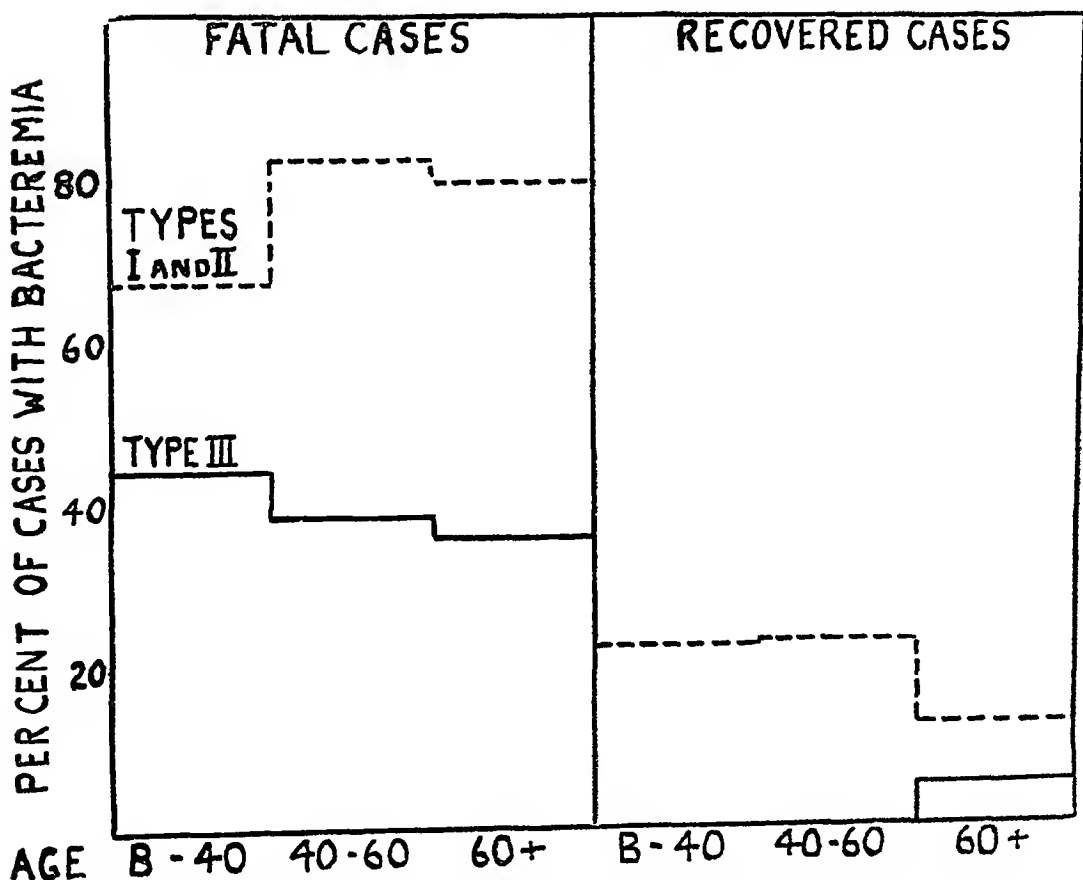


CHART 5 Relative incidence of bacteremia in pneumococcus types I and II pneumonia and pneumococcus type III pneumonia according to age

frequent in the type III infections than in the Is and IIs. Even more striking is the fact that the frequency becomes progressively lower with advancing age in the type III cases while the reverse is true with the Is and IIs. After 40 only a little over one-third of the fatal type III cases showed positive blood cultures while over 80 per cent of the Is and IIs had bacteremia. A similar contrast is presented in the non-fatal cases, a positive blood culture occurring only once among the type III cases, while positive cultures occurred with considerable frequency in the Is, occasionally in the IIs. It is probable, of course, that the considerable number of type I cases with positive blood cultures who recovered was influenced by serum treatment and that some of the type I pneumonias would otherwise have fallen in the fatal group. At any rate it is quite clear that type III pneumococcus invades the blood relatively infrequently, positive cultures being obtained in only 21, or 18.1 per cent of the 116 cases of type III pneumonia in which cultures were made as contrasted with 71 cases, or 36.6 per cent, with positive blood cultures in the type I series, and 32, or 40.5 per cent, in the type II.

The degree of bacteremia as well as the frequency was relatively slight in the type III infections. In the 21 cases showing positive blood cultures, the 45 cultures made showed 13 with no growth, 9 with growth in broth only, no colonies occurring on the pour plates, 14 with 1 to 10 colonies per cubic centimeter of blood, 5 with 11 to 32 colonies, and only 4 (in 3 patients) showed evidence of a heavy septicemia with more than 100 colonies

The time of invasion of the blood in the fatal cases is shown in chart 6, first in relation to day of disease in 45 cases in which the day of onset was definitely known, secondly, in relation to days before death in 53 of the 54 fatal cases, no blood culture being made in 1 case. The number of cultures per patient varied from 1 to 5. It is quite clear that bacteremia in the type III pneumonias of this study was in large part a late or terminal invasion rather than an early one.

The occurrence of complications shown to be due or presumably due to pneumococcus infection was not unduly frequent,—otitis media in 5 of the children, empyema in 1 child and in 4 adults, empyema and pericarditis in 1 adult, pericarditis and endocarditis in 1 adult, and thrombophlebitis in 1 adult. Other complications were staphylococcus suppurative parotitis, 1, cystitis (*B. coli*), 2, acute nephritis, 2, pyelonephritis, 1, non-suppurative arthritis, 1, and complicating hemolytic streptococcus infections, 5.

It has been shown in table 1 that the mortality in the series of type III pneumonias was 44.3 per cent, a figure closely comparable to that reported by others. That this high mortality is apparently not due to a highly virulent organism that invades the blood either early or frequently in the disease, nor to an undue prevalence of complications of pneumococcal origin has been brought out. Consequently other explanations must be sought. The first and most obvious reason is that a very large proportion of type III pneumonias occur in the later decades of life. The relation of age to mortality in this series is shown in chart 7, the

figures for the type I and the type II pneumonias being included for comparative purposes. From this data it is at once obvious that in the same age groups type II pneumonia had an equivalent or higher mortality than did type III pneumonia. Furthermore, the

mortality of type I pneumonia, even with serum treatment in the adults, was equivalent to that of type III pneumonia up to the age of 30 and approached it after the age of 45. There would seem to be little doubt from these results that the total high mor-

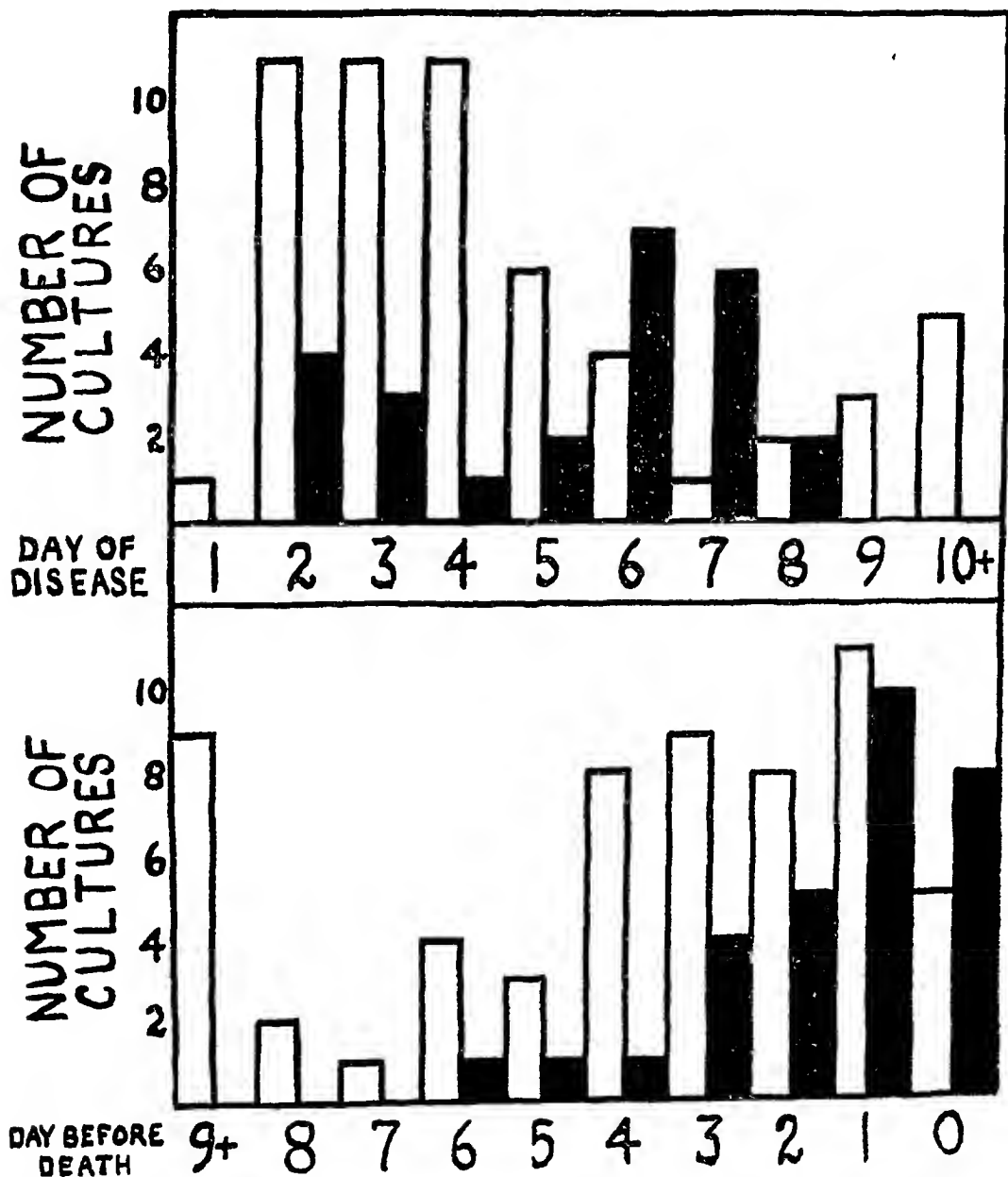


CHART 6 Bacteremia in fatal pneumococcus type III pneumonia in relation to day of disease and to day before death. Solid columns represent number of positive blood cultures, unshaded columns number of negative blood cultures.

tality shown by type III pneumonia is due in large part to the greatly preponderate incidence of the disease in the older age groups, rather than that it is due to an organism of particularly high virulence

The relation of chronic disease to the high mortality in type III pneumonia has been touched upon above and will be discussed now in more detail. In the first place it will be seen by reference to table 4 that 40 of the 119 cases in which data were available showed no evidence of chronic disease. Of these

only 6, or 15 per cent died, even though 13 of them were over 40 years of age. Of the 6 that died, 1 had a diffuse bronchiolitis (*H influenzae*) and focal pneumococcus type III pneumonia following whooping cough, 1 really died of agranulocytic angina with a terminal type III pneumonia, 2 had influenzal pneumonia with diffuse bronchiolitis, and 1 died of a complicating hemolytic streptococcus infection which developed 5 days after apparent recovery from the original type III pneumonia, thus leaving only one patient, a man of

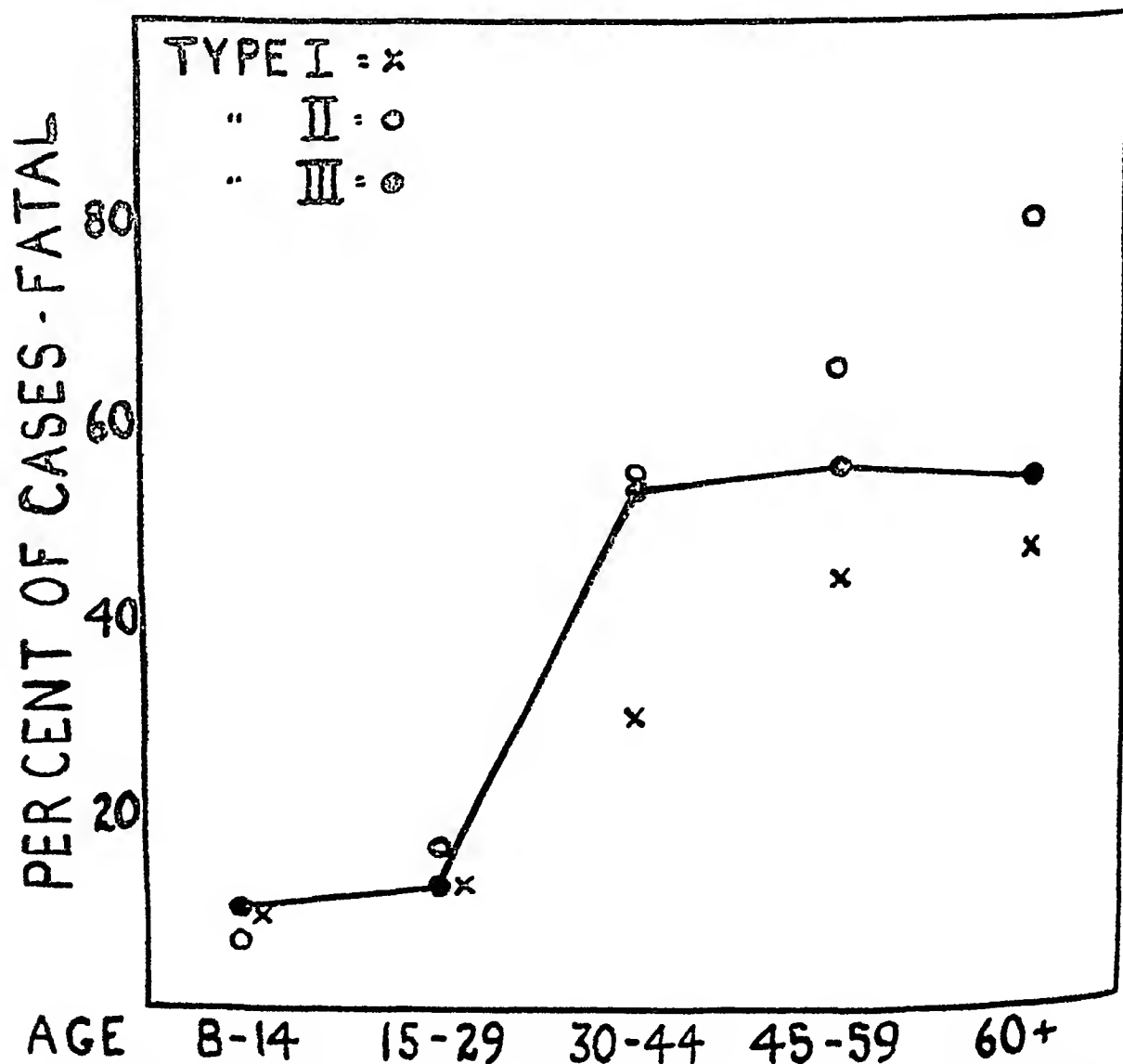


CHART 7 Mortality per cent in pneumococcus type I, in pneumococcus type II, and in pneumococcus type III pneumonia according to age

59, who died of an uncomplicated type III infection on the ninth day of the disease

Of particular interest is an analysis of the 9 fatal cases occurring under 40 years of age. The youngest patient was an infant under one year of age with pneumonia following whooping cough. The next was a boy of 14 with agranulocytosis, who developed a type III pneumonia 48 hours before death. The leukocyte count was 1000, with 4 per cent polymorphonuclear cells. The blood culture was positive. The next was a woman of 26 in the ninth month of pregnancy who contracted influenza which was complicated by pneumococcus type III pneumonia. She died on the sixth day. The blood culture was positive. The next was a woman of 31 who had suffered from chronic sinusitis and severe bronchial asthma with chronic bronchitis and emphysema for over a decade. She contracted pneumonia following an acute cold, was admitted on the fourth day of her illness and died on the fifth. The leukocyte count was 35,000, the blood culture negative. The next was a woman of 35 with exophthalmic goiter and syphilis with probable aortitis. She was admitted in a moribund condition and died within 36 hours. The leukocyte count was 58,000, the blood culture negative. The next was a woman of 37 in the third month of pregnancy who had been "sick for two weeks" before the onset of pneumonia. She was admitted on the third day and died on the seventh. The leukocyte count was 19,600, the blood culture negative. The next was a man of 39, a chronic alcoholic with arteriosclerosis and a

fairly marked secondary anemia. Red blood cell count was 3,300,000. Following a "bad attack of grippe" and getting soaked in a rain storm, he developed pneumonia. He was admitted on the second day and died on the seventh. The leukocyte count was 21,400, the blood culture negative. The next was a man of 39 with marked arteriosclerosis. Following a cold he developed pneumonia. He was admitted on the second day with a leukocyte count of 16,200 and a negative blood culture. He developed a marked leukopenia and positive blood culture on the fourth day and died on the fifth. The last was a woman of 39, showing no evidence of chronic disease who had severe influenzal pneumonia with diffuse bronchiolitis. She was admitted on the sixth day with a leukocyte count of 8,800 and a positive blood culture. She died on the ninth day. To continue further with the older patients would be mere repetition and serve no purpose. In order to emphasize the rôle of chronic disease in influencing mortality in this younger group it should be stated by way of contrast that only 4 of the 28 patients who recovered, showed evidence of chronic disease—rickets in a child of 3, chronic nephritis in a boy of 13, bronchial asthma in a boy of 20 and chronic bronchiectasis in a man of 37.

SUMMARY

A consecutive series of 122 cases of pneumococcus type III pneumonia admitted to the New Haven Hospital during the ten year period from Jan. 1, 1921 to Jan. 1, 1931, has been reviewed. Confirmatory of previous reports, it has been found that the inci-

dence is greatest in the later decades of life, approximately 50 per cent of the cases being over 55 years of age. Males were nearly twice as numerous as females. There was no special racial susceptibility found. The monthly incidence corresponded to that of pneumonia in general.

Acute predisposing causes played a very important part in the etiology of the disease, being of undoubted significance in 75 per cent of the cases. The most frequent predisposing causes were the acute respiratory infections—common colds, grippe, and influenza. These immediately preceded the onset of the pneumonia in 52 per cent of the patients. Exposure, exhaustion and acute alcoholism were recorded in 17 per cent. Chronic disease existed in 66 per cent of the patients and in all probability exerted a significant influence on susceptibility. Chronic pulmonary and vascular diseases, and chronic alcoholism were predominant.

The onset, the clinical course and the symptomatology of the disease were similar to those of other forms of pneumococcal pneumonia. In young adult life in otherwise healthy individuals the disease ran a mild course with early critical recovery. In the later decades the disease ran a more prolonged course and recovery by crisis was the exception.

Pneumococcus complications were of the usual frequency. Empyema occurred six times, pericarditis twice and endocarditis once. Otitis media occurred five times in children.

In spite of the high mortality bacteremia was found in only 18.1 per cent of 116 cases, in only 37 per cent of the fatal cases. In the latter it occurred mostly as a terminal invasion 24 to 48 hours before death. In only three cases was a high degree of bacteremia encountered.

Although the total mortality in this series was high, 44.3 per cent, it is shown that this was largely determined by the factor of late age incidence and by the prevalence of chronic disease at all ages in those who succumbed. In 40 cases not subject to chronic disease and irrespective of age, the mortality was only 15 per cent, while in 79 patients suffering from chronic disease (including 2 with pregnancy) the mortality was 56.9 per cent.

Finally, it may be concluded on the basis of the data here presented that pneumococcus type III pneumonia is a highly fatal specific infectious disease due, in general, not to a highly virulent organism that attacks and kills a healthy host, but rather to a debilitated, sickly or senescent host that succumbs to what is a relatively mild and uncommon infection in the young and vigorous.

REFERENCES

- ¹CICH, R. L. The etiology of pneumonia. *Am. Jr. Med. Sci.*, 1922, clxiv, 58-65.
- ²CORF, R. I. Acute pulmonary infections. DeLamar Lecture, 1928, Williams and Wilkins Company, Baltimore.
- ³STILLMAN, E. G. A contribution to the epidemiology of lobar pneumonia. *Jr. Exper. Med.*, 1916, xxiv, 651-670.
- ⁴STILLMAN, E. G. Further studies on the epidemiology of lobar pneumonia. *Jr. Exper. Med.*, 1917, xxvi, 513-535.
- ⁵CICH, R. L.; BALDWIN, H. S., and LARSEN, N. P. Lobar pneumonia, clinical and bacteriologic study of 2000 typed cases. *Arch. Int. Med.*, 1927, xl, 253-280.

Tularemic Pneumonia*†

By H H PERMAR, M D, and W W G MACLACHLAN, M D,
Pittsburgh, Pa

THE literature concerning tularemia became fairly extensive following the publication by Francis^{1,2} (1925-1926), of general articles on the subject, and especially after the papers of Francis and Callender³ (1927), of Goodpasture and House⁴ (1928), of Francis⁵ (1928), and of W M Simpson⁶ (1928). The latter articles contributed particularly to the knowledge of pathology of the disease. No attempt will be made here to review the history of tularemia, nor to discuss the literature, save as it concerns tularemic lesions of the lung. The papers of W M Simpson^{6,7} (1928-1930), contain excellent summaries of the more recent literature.

The case from which the materials were obtained for this study is, we believe, the twenty-fifth fatal case to be reported in this country, and the ninth to come to autopsy. A peculiar acute pneumonia was the outstanding finding.

CLINICAL HISTORY

The patient was a negro, aged 36, whose last employment had been in cleaning rabbits

*From the Departments of Pathology and Medicine of the School of Medicine, University of Pittsburgh, and the Pathological Laboratory and Medical Service, Mercy Hospital, Pittsburgh, Pa.

†Read before the Cleveland Meeting of the American Association of Pathologists and Bacteriologists April 2, 1931.

for market. On Monday, November 18, 1930, he cleaned a large number of rabbits and the same evening became nauseated and much fatigued. He was forced to leave his work on the following day as he was severely nauseated, although he did not vomit. He was dizzy and very weak. Later in the day he had a chill, was feverish and had a severe headache. He went to bed and remained there in this state until brought into the hospital on Saturday, November 23, 1930, the fifth day after the onset of symptoms.

On admission the patient appeared to be very toxic, the temperature was 105°F, the pulse 100, the respirations 28. There was some soreness in the right axilla but no enlarged glands were felt. A number of small, superficial cuts were noted on the palmar surface of the right hand, but there were no ulcers. The lungs were clear, although the case was considered at first as a possible pneumonia. The heart was normal. The blood pressure was 120/80, the pulse rate was relatively slow. The spleen was not palpable. The white cells were 7,125, with polymorphonuclear leucocytes, 47 per cent, large lymphocytes, 22 per cent, small lymphocytes, 23 per cent, large mononuclear leucocytes, 8 per cent. The urine was not remarkable. The blood culture was negative. On account of the history of contact with rabbits, blood was sent to Dr Edward Francis at Washington shortly after admission (seventh day of the disease), and the report was, "No agglutination with *B. tularensis*." The subsequent points of interest in the clinical course were as follows: delirium which was almost constant, incontinence of urine and feces, and continued high fever, with relatively slow pulse and respiration.

rates No cough or sputum was present although the patient said he spat up a little blood during the first few days of illness. There were no physical signs of pneumonia until two days prior to death (fifteenth day of the disease), when signs of consolidation were noted on the right side anteriorly, over the upper lobe. Hiccough was very persistent. The Wassermann test on the blood was negative. A later blood count (seventeenth day of disease) showed only 5,200 leucocytes, with polymorphonuclear leucocytes, 84 per cent, lymphocytes, 14 per cent, large mononuclear leucocytes, 2 per cent. There was no subsequent lymph-node enlargement, and on the seventeenth day of his disease blood was again sent to Dr. Edward Francis, who reported a positive agglutination (1-320) with *B. tularensis*. The patient died on the seventeenth day of his illness.

Autopsy

The outstanding autopsy findings were confined almost entirely to the lung, though typical tularemia lesions were also found in the peribronchial lymph-nodes and in the liver. The external appearance of the body offered nothing, save that the palms showed a few healing scratches. The axillary glands were not palpable.

Thorax. The thorax showed voluminous lungs and some pleural adhesions. There was only a slight acute pleural exudate, largely confined to the involved right lung, and chiefly to the right upper lobe, the site of the pneumonia.

The left lung weighed 350 gms, and the right, 950 gms. The lungs presented pleural adhesions, anthracosis and, in both apices, small old tuberculous scars. Both had some edema and congestion, especially in their lower lobes, and more intense in the right lung, the upper lobe of which felt firm and solid. The pleural surface of the right upper lobe was dulled by a film of yellow opaque fibrin, beneath which the interlobular divisions were evident as slightly elevated yellowish lines. On section, the tissue was generally consolidated, though the exudate was much denser along the bronchial tree, especially about the bronchioles and along the interlobular septa. The latter could be seen as opaque lines and they were most evident

in the peripheral parts of the lobe. Some of these lines were quite wide, and so edematous as actually to appear spongy or cystic in the gross. The bronchi, especially the smaller branches, were surrounded by dense, opaque, yellow-white, necrotic-looking areas which merged with the usual black peribronchial markings of anthracosis. The necrotic peribronchial foci were connected by consolidated lung which varied in color and consistency, but which in general had the gross character of gray hepatization. The bronchial tree contained a mucopurulent material that appeared thicker in the finer bronchioles. The larger vessels were clear. Thrombi were not seen on gross examination. The peribronchial lymph nodes showed slight enlargement and marked anthracosis. Their important lesion consisted of small white nodules of necrosis, with no fibrosis about them. There was also in one of the nodes a small area of caseation surrounded by fibrous tissue and showing a little calcification. No other nodes in the thorax or abdomen were found enlarged or similarly involved. The heart and pericardial sac revealed nothing abnormal. The aorta showed only a few superficial fatty streakings.

Abdomen. The peritoneal cavity had no abnormalities. The liver weighed 2,050 gms, and was the only abdominal organ showing notable change. Five or six tiny, pin-head sized, gray-white areas were found beneath the capsule, with neither fibrosis nor congestion about them. They had a depressed surface and appeared as small, clearly marked foci of necrosis of the liver substance, this appearance was borne out on cross section. No additional nodules were found on the cut surface of the liver. These lesions in the liver resembled those in the peribronchial lymph-nodes. In addition, the liver and kidney had undergone definite cloudy swelling. The spleen was congested and showed a typical recent white infarct.

The brain was not examined.

The heart's blood was sterile. No cultures were made from the lung. Direct smears showed moderate numbers of polymorphonuclear leucocytes, many mononuclear cells, often containing carbon granules, and much amorphous debris. No bacteria of any type could be demonstrated in the smears by

ordinary methods, and Ziehl-Neelsen stains showed no acid-fast organisms. No animal injection of tissues was done. The serum obtained on the seventh and seventeenth days of illness was injected into guinea pigs by Dr. Francis, with negative results.

Microscopical Findings

The microscopic changes in the lung, peribronchial lymph-nodes and liver were of particular interest. These organs all showed miliary foci of necrosis, identical with those found in animals and in acutely fatal human cases.

The sections of the involved portion of the lung presented typical miliary necrotic foci in the interstitial tissues. Certain of these lay in the walls of lymphatics, though as a rule they were simply scattered in the

stroma about the bronchial tree and vessels. The interstitial tissues were also the seat of an intense acute inflammation, characterized by extreme edema with much fibrin formation and a cellular exudate made up chiefly of large mononuclear leucocytes. The alveoli were extensively and diffusely involved in a pneumonia of serous and serofibrinous type. The predominating cell in the alveolar exudate was again the large mononuclear leucocyte. These cells tended to crowd the alveolar spaces and to become degenerated and necrotic, and the alveoli containing necrotic exudate also showed numbers of polymorphonuclear leucocytes. The characteristics of the mononuclear phagocytes which everywhere predominated in the cellular exudate were worthy of note. In the edematous interstitial tissues, in the



FIG. 1. Typical acute miliary tularemic lesion of liver.

dilated lymphatics, and in the adventitial and subendothelial zones of the vessels, they had generally a smaller size, with hyaline cytoplasm and a 'clock face' arrangement of the chromatin in the relatively large, eccentric nucleus. In a word, many resembled plasma cells, though all gradations could be found between these and typical mononuclear phagocytes. When they appeared free in the alveoli they were greatly enlarged, with foamy, vacuolated cytoplasm and relatively smaller nuclei that were often pyknotic. In the alveoli their phagocytic properties were most evident. They nearly all contained fragments of chromatin, lipid materials, degenerating erythrocytes, and varied quantities of carbon granules. The alveolar lining cells were swollen and quite prominent in the alveoli containing serous fluid and few inflammatory cells. They were less evident

where the exudate was more massive. It did not appear that the alveolar epithelium had desquamated to any appreciable degree.

Areas of necrosis of large groups of alveoli were a distinctive feature of the pneumonia. The necrosis involved the alveolar walls as well as the contained exudate. This change was the result of a striking lesion, involving both venules and arterioles and consisting of an acute inflammatory reaction of the subendothelial connective tissue with marked edema and swelling and an infiltration by mononuclear leucocytes. This, of course, resulted in great narrowing of the lumina, and as thrombosis tended to occur in many of the narrowed vessels, extensive necrosis of the lung tissue was inevitable. A similar but less marked change was present in the adventitia. These vascular lesions

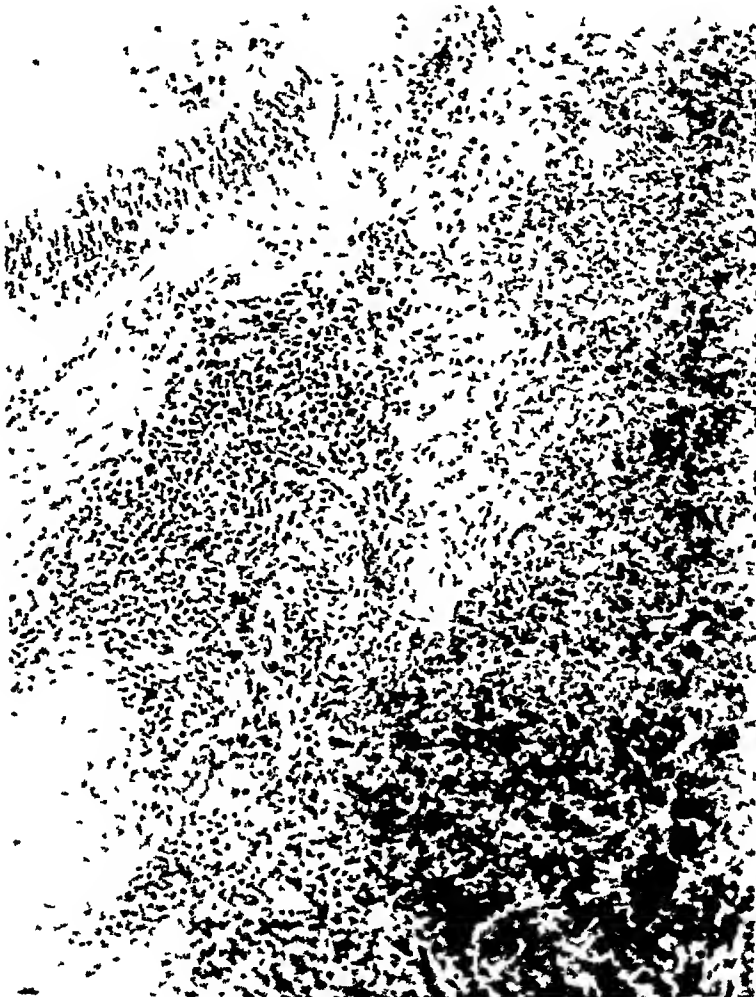


FIG. 2. Miliary necrotic tularemia foci in wall of bronchus. Note interstitial edema and inflammatory exudate.

were found only in the lobe showing pneumonia

The bronchial tree itself was affected particularly in the finer branches. Here the lumina contained masses of exudate like that in the alveoli, made up of mononuclear leucocytes, coagulated serum, fibrin and polymorphonuclear leucocytes. This exudate showed a tendency to necrosis, as did that in the alveoli. The mucosal linings of some of the bronchioles showed localized acute inflammation and even necrosis, which appeared to be a progression from the miliary necrotic foci in their interstitial tissues. It was noted that the mucosa of the larger bronchi revealed much less injury and exudate. The inflammatory reaction in the interstitial tissues was the outstanding feature of the reaction, while that in the bronchial tree was a

minor one, occurring by direct extension from the wall into the lumen.

The sections of the small focal liver lesions and of the similar but somewhat larger necrotic lesions of the peribronchial lymph nodes presented the characteristic acute necrotizing process that has been described by Verbruyck⁸, Francis and Callender³ and others, and therefore does not require elaboration here.

The infarct of the spleen gave the typical microscopic picture of a white infarct. This was in all likelihood the result of embolism from a pulmonary thrombus. No vascular lesions like those in the pneumonic lung were found in the spleen or other organs.

Fat stains (Sudan III) demonstrated moderate amounts of neutral fat in fine globules in the wandering mononuclear cells

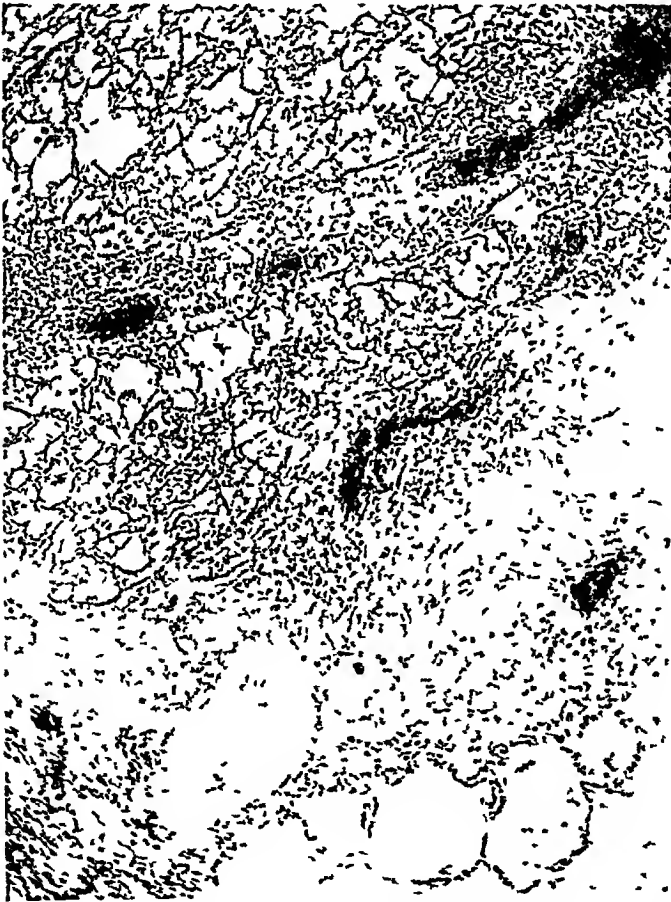


FIG 3 Extreme edema of stroma with fibrinous and mononuclear cellular exudate and serous exudate in alveoli

of the exudate, notably in the necrotic exudate. This was true in all the tularemic lesions, whether in lung, liver, or lymph nodes at the hilus of lung, but the striking fatty changes described by Palmer and Hansmann⁹ were not evident in the other organs. Controlled Ziehl-Neelsen stains on lung tissue showed no acid-fast organisms. Gram-Weigert and Giemsa stains for bacteria in the lung tissues revealed no organisms. The Brown-Brenn stain, which is especially useful for Gram-negative bacteria, showed no Gram-negative organisms, and no evidence of secondary infection.

DISCUSSION

The literature contains published reports of eight autopsies on fatal tularemia. In Francis' case¹⁰, the chest was

not prosected, though there was clinically a pneumonia. Verbrycke⁸ reported in the lungs typical acute tularemic nodules, the size of small shot, and one the size of a walnut. These had an associated bronchopneumonia in adjoining alveoli and bronchioles. Bardon and Berdez¹¹ described small necrotic patches involving several alveoli. The septal walls were necrotic. The necrosis resembled that of tuberculosis. Palmer and Hansmann's⁹ case presented what they termed an "inconsiderable" bronchopneumonia, but they noted unusual numbers of vacuolated mononuclear cells in the smaller vessels and wan-

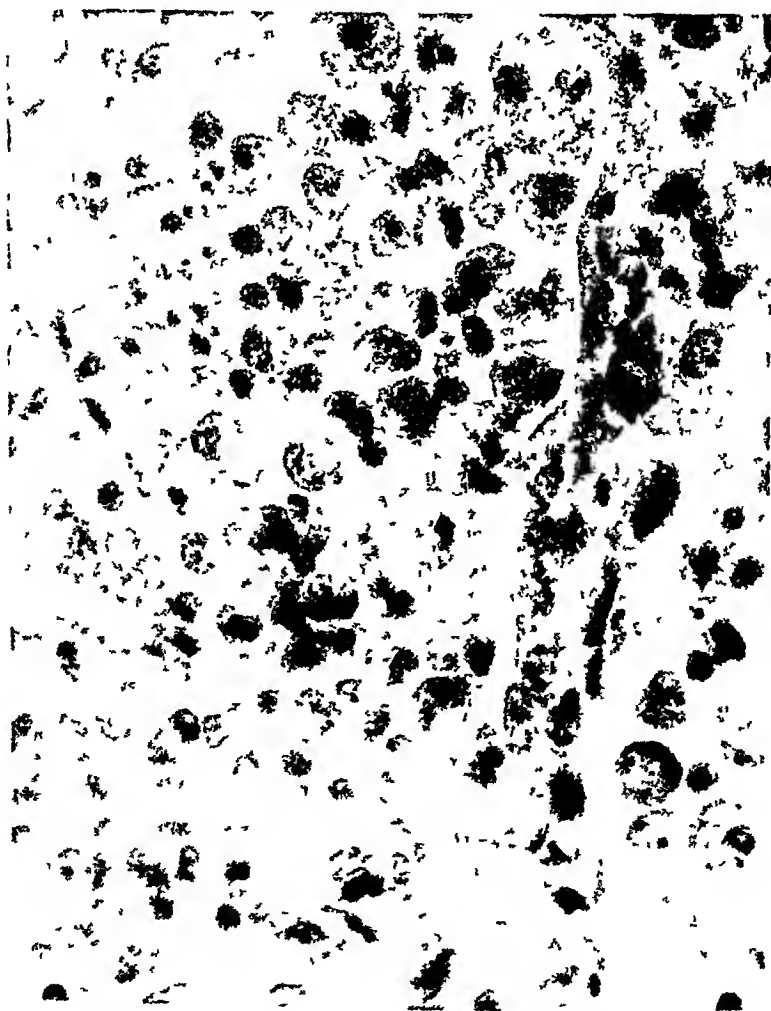


FIG. 4. Mononuclear phagocytic cells in the alveolar exudate.

dering into the alveoli. Bunker and Smith¹² found a marked bronchopneumonia, with extensive necrosis of the alveolar walls as well as of the free exudate. The cellular exudate consisted chiefly of polymorphonuclear leucocytes, though many lymphocytes and endothelial cells were present. The peribronchial lymph-nodes in all the foregoing were reported as showing typical tularemic granulomatous foci, in either the acute or the sub-acute stage. W. M. Simpson's⁶ case, the most acute to come to autopsy, had no pneumonia, but two typical

acute tularemic nodules were found in the lung tissue. The case of Goodpasture and House¹ showed only a localized pleurisy with a mononuclear cell exudate, near the enlarged peribronchial lymph-nodes. In Bruecken's³ case (in which the patient had recovered from a pneumonia in the early weeks of the disease), the lungs were found clear at autopsy when death from chronic glandular tularemia finally occurred five months after the onset.

In brief then, seven out of the eight cases in which the thorax was prosected (87.5 per cent) presented



FIG 5 Subendothelial edema and mononuclear cellular exudate in intima of pulmonary vessel. Serous and fibrinous exudate in adjoining alveoli with necrosis of lung tissue and the contained exudate.

tularemic lesions of some type in the lung; and in five of the eight (62.5 per cent) there was diffuse pneumonic involvement. Of all the reported fatal cases, now numbering twenty-five, nine (36 per cent) showed pneumonia either clinically or at autopsy.

The present case report indicates that an infection by *B. tularensis* occurred without demonstrable localized granulomatous ulceration on the skin and without regional lymphatic involvement. In the absence of peripheral localized tularemic lesions in either

the skin or lymphatics, one must consider here the possibility of primary respiratory tract infection, with direct interstitial invasion of the lung. The mode of infection of the lung cannot be determined from the data available, but the case is of value since it gives an opportunity to describe in detail the pulmonary lesions.

The presence in the stroma of the lung of the typical miliary necrotic focal lesion is the most significant single finding, from the standpoint of identifying the pneumonia as of tulare-



FIG. 6. Thrombosis of pulmonary vessel showing subendothelial edema and mononuclear cellular exudate. Necrosis of the surrounding lung alveoli and the contained serofibrinous exudate.

mic origin. The other outstanding feature is the extreme subendothelial edema and mononuclear cellular infiltration in the blood vessels. This latter observation has not been recorded previously. It is of considerable interest, as we believe this vascular lesion with the associated thrombosis in the affected vessels, explains the peculiar necrosis that has been noted in tularemic lung inflammations. The usual proliferative and obliterative changes in the smaller vessels and capillaries, which were first described in tularemic lesions in the human by

one of us (Permar and Weil¹³), and subsequently by Francis and Callender³, and others, are not present, probably because of the rapidly fatal course of the disease. The predominance of mononuclear leucocytes in the cellular exudate is evident in this case, as in most of those previously described.

We believe that we have demonstrated a pneumonia with morphologic changes which are presumably specific for tularemia and recognizable with reasonable certainty in the absence of a suggestive history or of a positive agglutination test. It is of course to



FIG 7. Small bronchiole with a mononuclear cellular exudate. A more active process present in the surrounding lung tissue.

be kept in mind that the duration of the disease may well alter somewhat certain phases of the microscopic reaction. Further, we are not aware of a pulmonary inflammation occurring in any other infectious disease that has exactly the characters described here.

As to the clinical importance of lung involvement in tularemia, we agree with Francis^{5,14} who has stated that a pulmonary lesion indicates a serious prognosis. This is borne out by the high incidence of pneumonia in fatal cases. We would emphasize that the history of contact with carriers of *B. tularensis* (most commonly wild rab-

bids), is very important in the diagnosis and further, that the agglutination test is necessary for absolute confirmation. It must be kept in mind, as indicated by this case, that a positive agglutination test may not be developed early in the disease.

SUMMARY

The case of tularemia which forms the basis of this report was remarkable in that there was neither a peripheral ulcerative lesion nor regional lymphadenitis. The outstanding clinical manifestations were a markedly toxic state and an atypical pneumonia.



FIG. 8. Large bronchiole with the wall intact, and containing a little serous exudate and a few mononuclear phagocytes.

Tularemia was suggested by the history of handling dead wild rabbits and was confirmed by a positive agglutination test for *B tularensis* on the patient's blood serum

At autopsy, the gross findings in the lung were unusual, indicating an acute lobar pneumonia with much interstitial inflammation and necrosis. The lesion suggested an acute diffuse reaction of granulomatous type.

The histopathologic lesion was essentially an interstitial pneumonia, distinguished by multiple miliary necrotic foci throughout the stroma of the diseased lobe. These necrotic foci were identical with those seen in an acute diffuse tularemic infection. An intense and widespread inflammatory edema accompanied the development of the specific tularemic nodules in the lung. The blood vessels of the affected lobe showed great edema of the subendothelial and adventitial connective tissue, with an infiltration of mononuclear leucocytes into these coats. This involvement of the vessels produced much narrowing of their lumina, and complete occlusion by thrombosis was often found. Areas of necrosis of considerable size and irregular outline

were a striking feature of the microscopical findings. This necrosis was associated clearly with the vascular lesions just described, and appeared to have been caused directly by the vascular narrowing and occlusion.

Thus it may be stated that when a diffuse pulmonary involvement occurs in the course of a tularemic infection, the prognosis must be grave, as acute tularemic inflammation of the lung is a progressively destructive lesion. This is borne out by the data available on fatal tularemia.

The authors take pleasure in availing themselves of this opportunity to express their thanks to Doctor John M. Johnston of Pittsburgh for his kind assistance in the preparation of the microphotographs illustrating this paper.

Since this paper was written, the authors have learned from Dr. Edward Francis of the Public Health Service, National Institute of Health, Washington, D. C., that four other autopsy reports, two with prominent lung lesions, are in process of publication, and Hartman of Detroit reported before the American Association of Pathologists and Bacteriologists, April 2, 1931, an autopsy on tularemia with interstitial tularemic pneumonia among the findings. These cases add somewhat to the evidence that pulmonary tularemia has a grave prognosis.

REFERENCES

- ¹FRANCIS, E. Tularemia, Jr. Am. Med. Assoc., 1925, lxxxiv, 1243.
- ²FRANCIS, E. Tularemia. Second Ludwig Hektoen lecture of the Billings Foundation, Proc. of Inst. of Med. of Chicago 1926.
- ³FRANCIS, E., and CALLENDER, G. R. Tularemia: the microscopic changes of the lesions in man, Arch. of Path., 1927, iii, 577.
- ⁴GOODPASTURE, E. W., and HOUSE, S. J. The pathologic anatomy of tularemia in man, Am. Jr. Path., 1928, iv, 213.
- ⁵FRANCIS, E. Symptoms, diagnosis and pathology of tularemia, Jr. Am. Med. Assoc., 1928, xci, 1155.
- ⁶SIMPSON, W. M. Tularemia: study of rapidly fatal case, Arch. of Path., 1928, vi, 554.
- ⁷SIMPSON, W. M. Recent developments in tularemia (Francis' disease), Jr. Lab. and Clin. Med., 1930, xv, 311.
- ⁸VLEBRICKE, J. R. Tularemia, with report of a fatal case simulating cholera, with post-mortem report, Jr. Am. Med. Assoc., 1924, lxxxii, 1577.

- ⁹PALMER, H D, and HANSMANN, G H
Tularemia report of a fulminating case
with necropsy, Jr Am Med Assoc,
1928, xc1, 236
- ¹⁰FRANCIS, E The occurrence of tularemia
in nature as a disease of man, Pub
Health Rep, 1921, xxxvi, 1731
- ¹¹BARDON, R, and BERDEZ, G Tularemia
report of a fatal case with post-mortem
observations, Jr Am Med Assoc, 1928,
xc, 1369
- ¹²BUNKER, C W O, and SMITH, E E
Tularemia report of four cases, one
fatal, with autopsy report, U S Nav
Med Bull, 1928, xxvi, 901
- ¹³PERMAR, H H, and WEIL, G C The
histopathology of the subcutaneous
lesions in tularemia in man, Am Jr
Path, 1926, 11, 263
- ¹⁴Personal Communication from Dr Edward
Francis

Experimentally Produced Lesions of the Liver*†

By JESSE L. BOLLMAN, M D, and FRANK C. MANN, M D,
Rochester, Minnesota

MANY problems of clinical medicine have been clarified by experimentation on animals. This method has numerous advantages in that most of the factors which enter into the production and progression of abnormal processes are capable of exact control. Although it is not as yet possible exactly to simulate in animals all of the types and phases of hepatic disorders, it is possible to produce experimentally most of the abnormal conditions usually associated with hepatic disease in human beings. With our associates we have studied a large number of animals following various procedures which have directly affected the liver, and it is from these animals that we have drawn our conclusions concerning the physiology and pathology of the liver.

Perhaps our most valuable data have been obtained from animals following complete removal of the liver,^{2,4,6,7,9,11,12,14,15,20,21} but since most of the facts of this series are well known, only brief mention of them will be given here. After proper preliminary measures to eliminate complicating factors

such as portal stasis, the liver may be completely removed and the signs of complete hepatic insufficiency may be observed. Because the liver alone adds glucose to the blood, hypoglycemia is the first definite symptom referable to the absence of the liver. Fortunately, in the human being only the rare case of extreme acute atrophy of the liver presents this symptom. If hypoglycemia is prevented by the administration of glucose the liverless animal presents no unusual symptoms for twenty-four to forty-eight hours, at which time a characteristic set of symptoms develops and death from complete hepatic insufficiency follows. These symptoms are loss of hearing, loss of vision, loss of reflexes, muscular rigidity, coma, convulsions, and death, progressively occurring in the order mentioned, the entire course usually lasts from thirty minutes to four hours. We know of no hepatic disease in which these symptoms are exactly reproduced, although several of them are noted in fatal cases of supposed hepatic insufficiency. In addition to loss of the power of forming sugar, the liverless animal also loses the power of forming urea, of destroying amino acid and uric acid, and of effecting other metabolic changes for which the liver is essential.

*Read at the Baltimore Meeting of the American College of Physicians, March 23 to 27, 1931.

†From the Division of Experimental Surgery and Pathology, The Mayo Foundation, Rochester, Minnesota.

It would appear that any test⁸ capable of measuring the metabolic changes which depend entirely on the liver would give an accurate index of the efficiency of this organ. There are several reasons why such tests show but little, and studies of animals from which the liver has been partially removed reveal some of the reasons for failure of these tests. In the dog, and in many other animals, the liver consists of several distinct lobes, one or more of which may be successfully removed. Immediately following such operations the remaining portions of the liver begin to hypertrophy and by serial operations removing a lobe of liver every few weeks, it is possible to remove more hepatic tissue than was originally present and still have a normal weight of hepatic tissue remaining in the dog. Even the liver of the normal adult dog is capable of restoration of more than 100 per cent of its weight. During this process no signs of hepatic deficiency are observed except a transient upset of a few days duration which probably is due to injury of the remaining hepatic tissue rather than to actual deficiency because of removal of tissue.

It is possible to prevent this restoration of liver following partial removal, and each of the three methods I will describe have their counterpart in most cases of chronic disease of the liver. Restoration of hepatic tissue is greatly reduced or completely absent in the presence of obstructive jaundice¹², in the presence of marked cirrhotic changes in the liver, or when the portal blood supply to the liver has been reduced, as by an Eck fistula¹⁰. When one of these three conditions is present

partial hepatectomy may be performed without subsequent increase in the size of the remaining part of the liver. With these methods animals may be maintained by proper dietary precautions with less than twenty per cent of the normal amount of hepatic tissue. These animals show surprisingly little evidence of decreased hepatic efficiency by any of the functional tests which we have employed. It is obvious that less than twenty per cent of the liver can accomplish the work of the entire organ.

Animals with complete obstructive jaundice caused by ligation of the common bile duct show many signs which are familiar to the physician. For the first few days the liver is enlarged, but it soon becomes smaller than normal, and there is rather extensive atrophy of hepatic cells. Under ordinary conditions the jaundiced dog does well for a few weeks, but after this time many interesting phenomena may appear. In the first place, a diet rich in carbohydrate becomes increasingly more necessary for the maintenance of these animals, we use milk bread, and syrup. After two or three months a diet exclusively of meat, if taken, will prove fatal within about one week, but with a diet high in carbohydrates life may be prolonged for at least a year. Abdominal and esophageal varices develop and hemorrhage into the gastro-intestinal tract is of frequent occurrence. Duodenal ulcer¹¹ occurs in an extremely high percentage of cases. Ascites develops spontaneously in the later periods of obstructive jaundice, and may be produced and relieved experimentally at an earlier period by dietary measure.

Infectious cirrhosis, experimentally produced, is very similar to that rather infrequent type as seen in man. Following experimental cholecystenterostomy¹ there is an ascending infection of low grade involving the biliary ducts. After several months the gross appearance of the liver is not unlike that in the usual type of nodular cirrhosis, and on the cut surface of the liver are seen marked thickening and dilatation of the bile ducts, with marked cicatricial changes. Microscopic examination discloses that the infective process has encroached on the hepatic parenchyma and there is infiltration with leukocytes, and later with round cells. There are definite zones of fibrous tissue surrounding the biliary ducts and in this there are many proliferating small bile ducts which present a picture suggestive of canalization such as that which occurs in a thrombosed blood vessel. Animals with infectious cirrhosis have no definite symptoms until the liver is extensively involved. Gastro-intestinal upsets, diarrhea, vomiting, and occasional melena, are usually the first symptoms noticed. With progression and continued attacks of gastro-intestinal bleeding, definite anemia usually develops, and a small amount of ascitic fluid may be present before death. Jaundice has not been observed, except as a terminal event.

To produce an experimental picture similar to the usual type of portal cirrhosis, it is necessary repeatedly to administer sublethal doses of a toxic agent which produces acute necrosis of the liver. We have used carbon tetrachloride and tetrachlorethane. The latter was extensively used as a solvent

for waterproof aeroplane paint before it was discovered that many workers with this poison contracted subacute yellow atrophy or cirrhosis. The method of administration to experimental animals determines somewhat the character of the lesions produced. If the material is injected into the spleen repeatedly, extensive atrophy of the left side of the liver occurs and there is marked hypertrophy of the right lobes of the liver. Injection of the material by peripheral vein or subcutaneously and also oral administration, is followed by more or less diffuse acute necrosis, with subsequent permanent changes in the liver. These changes also represent atrophy and hypertrophy but are found in close proximity in all portions of the liver. Consequently hypertrophic or atrophic cirrhosis may be produced, depending on the predominance of hypertrophy or atrophy. With increasing injury to the liver these animals have most of the symptoms characteristic of portal cirrhosis. Gastro-intestinal upsets, diarrhea, and intestinal hemorrhage are usually the first symptoms observed, and definite retention of dye may be detected. With continuation of administration of the toxic agent, slight jaundice may be produced, and finally marked ascites may develop. Few of these animals die of actual hepatic insufficiency; many have died following excision of a small piece of liver for histologic examination, a procedure that is relatively harmless to the normal animal. Many die following extensive gastro-intestinal hemorrhage, and in many chronic or subacute duodenal ulcer develops, with subsequent perforation and peritonitis. We have lost a large

number of animals following repetition of administration of the toxic agent. The necrosis produced seems to be more extensive as the liver becomes more severely injured, and a picture similar to that of subacute yellow atrophy frequently results. It should be noted that repetition of administration of the toxic agent is necessary, since this type of lesion is not progressive, and the animals improve considerably when the toxic agent is removed.

The chronic lesions of the liver we have been able to produce depend on the acute lesions repeatedly produced. Changes are not observed with frequent doses which are so small that acute necrosis is not produced. If doses that are too large are used, extensive necrosis results, from which the animal does not recover. The extent of acute hepatic injury obviously depends on the amount, toxicity, and specificity of the toxic agent used. In this respect it may be noted that we have been unable to produce hepatic necrosis with alcohol alone, but the addition of alcohol to several toxic substances produced much more extensive lesions. This increased toxicity may be due to the fact that most of these toxins are soluble in alcohol and that the effective dose is greatly increased when they are absorbed with the alcohol. Additional reasons for increased necrosis may be found in the fact that alcohol injures the liver so that it is unable to combat additional poisons. There is considerable evidence that the extent of hepatic injury also depends on variations in the more or less specific resistance of the liver to injury. In dogs much more exten-

sive lesions are produced by chloroform¹⁸ or carbon tetrachloride⁵ when the animals are maintained on a meat diet than if they are maintained on a diet high in carbohydrate and rich in calcium. The difference in activity of the hepatic cell appears to be correlated with the amount of glycogen in the liver and is less when the fat is more predominant. In this respect it should be noted that there is a cycle¹⁹ of changes in the glycogen and fat content of the liver, daily, with relation to the time of meals. Toxic agents are much more effective when administered to the fasting animal than when administered even several hours after the taking of food. Impairment of circulation in the liver increases the effectiveness of many hepatic poisons. After exclusion of the portal blood from the liver by an Eck fistula, carbon tetrachloride is more than ten times as effective as similar doses given to normal animals.

Many animals with considerable necrosis and with fatty changes in the liver show no symptoms, but when necrosis is more extensive, gastro-intestinal upsets, jaundice, and a small amount of peritoneal fluid may be noted. If further toxin is not administered, and if the necrosis is not too extensive, reparative processes begin in a short time. Within twenty-four hours there is marked leukocytic infiltration, and lymphocytes predominate later. The disintegrated hepatic cells appear to be removed by phagocytes, and their place is taken by new hepatic cells which have arisen by division of the adjacent uninjured hepatic cells. There is also a proliferation of fibrous tissue, apparently arising from that around the

portal spaces. Repetition of this process may give rise to extensive scarring of the liver, such as is seen in typical portal cirrhosis. Hypertrophic nodules develop, apparently by division of a few hepatic cells into many cells in a restricted area, so that lobular arrangement is not possible, and these islands of hepatic cells show little relationship to the blood vessels and biliary ducts of the liver.

In general, it may be said that the reparative processes of the liver tend to restore that organ to normal appearance, and it is surprising to see that after extensive injury, restoration of the liver may be so effective that the organ appears quite normal. Continual repetition of the process, however, gives rise to cirrhosis in which the size of the liver depends on the predominance of hypertrophy of the hepatic cells, or their absence due to the extensive cicatricial changes.

Our observations on experimental animals may be summarized best by considering those processes which in general appear to affect the response of the animal to the alterations in pathologic changes in the liver. One of the most striking observations, already referred to, is that the liver possesses huge reserve as evidenced by the extreme amount of liver that may be injured or removed without the production of any symptoms referable to the liver. Actual removal of as much as eighty per cent of that organ is not attended by a measurable loss of hepatic function, and sufficient liver remains to enable the animal to carry out all of its normal life and to appear to be well. In addition to the fact that less than twenty per cent of the normal

liver is necessary, the liver is capable of more than 100 per cent replacement due to the restoration of tissue. These observations appear to offer a definite explanation for the fact that the classical signs and symptoms of cirrhosis do not appear until the liver has been almost completely worn out by the repeated attacks of some toxic agent. It is to be noted, also, that the three factors which prevent restoration and repair of the liver in the experimental animal are each present in cirrhosis, that is, more or less extensive cicatrization of the liver, reduction of the actual blood supply to the liver, and jaundice. That cirrhosis is not entirely a hopeless condition, however, appears from the observation that animals with extensive cirrhosis, ascites, and jaundice do not continue to progress downward, but recover from their symptoms when the toxic agent is removed and a diet high in carbohydrate is administered.

The development of collateral circulation in the experimental animal appears similar to that found in the human being. In extensive cirrhosis from toxic agents, obstructive jaundice of long duration, or uncompensated extensive removal of hepatic tissue, the veins of the entire portal region are found to be dilated, and varicosities develop in the esophageal veins and in the abdominal wall. Hemorrhage into the gastro-intestinal tract is of frequent occurrence, but massive fatal hemorrhage is less common. Most animals with extensively injured livers have tarry or bloody stools and definite anemia. This intestinal bleeding is seldom continuous, usually it occurs in attacks lasting from two to ten days.

after which there are spontaneous remissions of short duration. In some animals a subacute or chronic duodenal ulcer develops from which hemorrhage may occur. Studies of the blood of these animals fail to show any definite alterations in the known factors concerned in coagulation. It is obvious that the control of coagulation is less stable than normal when the liver is extensively injured. Values for blood fibrinogen and blood platelets may at times be found to be low, but later, in the same animal, may be normal. Coagulation time and clot retraction time are likewise variably found to be delayed or normal. Obviously, other factors affect the coagulation of the blood in addition to the definite, although vague, influences of the liver. That the hepatic factor, however, plays a definite part in the hemorrhages, is evidenced by the fact that we have never observed this type of bleeding in dogs prepared for removal of the liver in three stages. In this method both the vena cava and the portal vein are occluded below their entrance into the liver and there is extensive collateral circulation sufficient to return both caval and portal blood to the heart, the liver is only slightly injured, if at all, and bleeding or a change in the factors of coagulation does not occur. Recovery of animals from extensive hepatic injury is accompanied by recovery from this hemorrhagic tendency, although the collateral circulation may not appear to be altered.

Since a small amount of hepatic tissue is sufficient to maintain the normal functions, both metabolic and excretory, of that organ, it does not appear surprising that most functional

tests fail to indicate hepatic pathologic changes until they are extensive. Many of the metabolic tests which have been devised are influenced by the previous diet and the condition of the other organs of the body, as well as by the condition of the liver. This is particularly true of a number of tests devised to determine the activity of the liver in carbohydrate metabolism, and some of these we have found to give similar results when applied to a normal animal as to one completely deprived of its liver. Tests based on the activity of the liver in the metabolism of protein give the anticipated results in entire absence of the liver but deviation from normal is not appreciable in cases of hepatic injury unless the injury is extreme. In most of our experiments on rapidly failing animals failure of protein metabolism was present, and usually the fatal termination ensued in a few days. Quantitative estimation of the detoxicating power of the liver, particularly with salicylates, camphor, compounds of phenol and so forth, have not been satisfactory in our hands. We have distinct evidence that many of these compounds are conjugated partially or completely in the entire absence of the liver. The guanidine¹⁷ content of the blood may be definitely elevated in the presence of acute intoxication with extensive hepatic necrosis, but it rapidly returns to normal without giving any indication of the amount of permanent injury to the liver.

Tests designed to evaluate the excretory function of the liver appear to be the most satisfactory of any hepatic tests we have used. Failure of this function is indicated by bilirubinemia,

this is not observed in the experimental animal without biliary obstruction unless extensive hepatic injury is present. Acute hepatic necrosis is usually accompanied by bilirubinemia of a degree approximately parallel to the extent of the hepatic injury. In acute and chronic hepatic injury, the van den Bergh reaction is direct. Extensive lesions of the liver also produce definite delay in the excretion of bilirubin and other chromogenic substances which may be injected intravenously. We have recently determined the retention of bromsulphthalein in a series of dogs with varying degrees of experimentally produced cirrhosis. Several tests were made prior to surgical exploration and biopsy, and several tests were made after this procedure, before additional carbon tetrachloride had been administered to produce more extensive cirrhosis. In each animal the degree of retention of dye was compared with the gross and microscopic appearance of the liver. For the most part, there was very satisfactory correlation between the degree of injury to the liver, as estimated from the gross appearance and histologic section, and the degree of retention of dye. There were, however, exceptions in sufficient numbers to demonstrate clearly that the last word is yet to be said regarding the function of the liver and its pathology. A few animals with extensive cirrhotic changes, usually hypertrophic, gave no evidence of retention of dye, although few normal-appearing hepatic cells could be demonstrated histologically. A few normal animals, with no demonstrable hepatic lesions, gross or microscopic, showed marked retention

of dye. It should also be mentioned that a few livers, which microscopically appeared to be definitely cirrhotic, appeared grossly to be normal.

Ascites develops spontaneously in animals with very extensive cirrhosis, and also following obstructive jaundice of long duration. Under both of these conditions we have been able to produce and remove ascitic fluid by dietary measures. Animals with obstructive jaundice were maintained for three or four months on a diet of milk, bread, and syrup and showed no evidence of ascites. They were then fed meat for three or four days. In most animals the presence of ascites could be determined by inspection of the abdomen within twenty-four hours after the feeding of meat was instituted. It was not uncommon for the abdominal circumference of an animal weighing five to seven kilograms to increase from an original measurement of about 35 centimeters to more than 50 centimeters, and from one to three liters of fluid could be aspirated from the peritoneal cavity. In many animals this process was repeated several times. Certain animals appeared more resistant than others, but in all ascites developed within four days of the initiation of repeated feeding of meat. In a few experiments the animals refused to eat meat in any form, and feeding by stomach tube was not very successful. Most of the animals that were refractory to formation of ascitic fluid became less so as the interval following complete biliary obstruction increased, and with repetition of the regimen of meat feeding. As the process was repeated more and more ascitic fluid could be formed with small-

ler and smaller intake of meat. Experimental cirrhosis must be very extensive before ascites can be produced in this way, but if the cirrhosis is extensive enough feeding of meat will produce ascites.

The active substance which produces ascites in these animals is probably not

liters of newly formed ascitic fluid can be withdrawn. Control experiments with the addition of salt to the diet have produced entirely negative results.

The ascites disappeared in most instances when the meat or the meat extract was withdrawn from the diet.



FIG. 1. Atrophy and hypertrophy of the liver. In the upper row are the lobes of a dog's liver three years and three months after a series of injections, lasting three months, of small amounts of carbon tetrachloride into the spleen. In the lower row are the lobes of a normal liver of the same weight removed from a normal dog of the same size. Hypertrophy of the right lateral lobe and atrophy of the other lobes may be noted. This condition is not changed from that seen at exploration two and a half years previously.

protein. Proteins of milk do not favor the production of ascites. The active principle appears to be in the water-soluble extractives of meat. The feeding of meat extract which is free from protein and fat produces results which are even more striking than the feeding of meat. Within four to six hours after feeding twenty-five grams of meat extract to animals with obstructive jaundice of long duration, or with extensive cirrhosis, marked abdominal distention is evident and two or three

The substitution of large amounts of carbohydrate to the diet seemed to aid in the removal of the fluid; the fluid disappeared more rapidly than when all food was withheld. With repetition of the formation and removal of ascitic fluid, the animals became more susceptible to accumulation of fluid, and the time of disappearance of the fluid with the feeding of glucose became greater and greater. The mercurial diuretics, given in small doses, were also effective in reducing the as-

cites, but these too became less effective after several administrations. Transfusion of blood into those animals with ascites that showed definite evidence of anemia, and in some instances, also, definite reduction of the values for plasma protein, were effective in removal of ascitic fluid. Transfusion was not effective in the animals with ascites if these changes in the blood were not present. In all of our experiments the progressive loss of resistance to the accumulation of ascitic fluid was accompanied by increased in-

jury to the liver, either by the increasing duration of biliary obstruction or by continuation of administration of carbon tetrachloride.

The mechanism by which meat extract produces ascites in these animals is not understood. In the animals in which it does produce ascites there does not seem to be any alteration in the control of peritoneal fluids prior to the administration of the extract. If saline solution or ascitic fluid, either from dogs or men, is injected into the peritoneal cavity of dogs, it is absorbed



FIG 2 Experimental cirrhosis from carbon tetrachloride. The liver of a dog which had received 100 doses (5 cc each) of carbon tetrachloride over a period of two years.

as rapidly by animals which are in the pre-ascitic stage as by normal animals. It would appear that meat extract might produce ascites by one of three possible mechanisms, none of which is proved (1) because of a specific colloidal effect on the blood or vessels which enables water to diffuse into body cavities more readily than

normally, (2) a specific effect on the liver, which produces constriction of the intrahepatic portion of the portal system with subsequent sufficient increase in portal pressure to produce vascular changes in the abdominal viscera, or (3) specific irritation of the peritoneal surfaces, which increases the secretion of fluid from these surfaces



FIG. 3. Hypertrophic cirrhosis with subsequent atrophy. Size of the liver of dogs with peritoneoperitoneum, *a*, normal animal of the same weight and size as that illustrated in *b*, *c* and *d*, *b*, marked hypertrophy which occurred in one year in which the animal received 150 (1 cc. each) of tetrachlorethane, *c*, same animal as that shown in *b* sixteen days later, *d*, same animal as that shown in *b* and *c* after twenty-eight more days. Additional tetrachlorethane is not given and within three months the liver had returned to normal size.

and inhibits their absorption of fluid. It is to be noted that in any case, extensive injury to the liver must be present, so that it appears obvious that a normal liver must compensate for, or detoxify, this active agent which will produce ascites when the liver is extensively injured.

In all of our experimental work, the proportion of carbohydrate in the diet of animals with extensive hepatic lesions is of outstanding importance. In the entire absence of the liver, animals succumb to hypoglycemia unless glucose is given. We have maintained dogs with complete biliary obstruction for six to twelve months on a diet of milk, bread, and syrup, and have repeatedly observed the rapidly fatal effects of diets composed entirely of meat. After biliary obstruction has been present for three months we have

been unable to cause a dog to survive on a diet entirely of meat for more than six days. The protective value of carbohydrates against hepatic injury from toxic agents is well illustrated by the following experiment.

Four dogs were maintained on a diet of milk, bread, and syrup, and four on a mixed diet, containing about 25 per cent meat protein, 50 per cent carbohydrate, and 25 per cent fat, four other dogs received as much meat as they desired. All of these animals received daily doses of 10 cc of carbon tetrachloride by mouth. At the end of one month, one of the animals that was fed meat had marked ascites and died two weeks later. Within three months ascites developed in one of the remaining animals, which later died, and the other two meat-fed animals were distended with ascitic fluid. In the same period of three months, the other eight dogs remained in good condition and showed no signs of ascites. Biopsy revealed that the livers of the animals to which meat had been fed suffered more extensive injury than was



FIG. 4. Hypertrophic cirrhosis, specimen removed from dog the day the routine program shown in figure 3 b was taken.

present in the other animals, although lesions with the definite appearance of cirrhosis were present in all

Glucose is of definite value following surgical procedures on animals with extensively injured livers. Following operation, these animals are markedly lacking in resistance, and extensive degenerative changes rapidly occur in the injured liver. Intravenous injection of large amounts of glucose appears to enable many animals to recover that would almost certainly succumb had the glucose not been given. This same specificity for glucose appears in animals suffering from acute intoxication following excessive administration of hepatic toxins.

SUMMARY

From our experimental studies of animals with definite pathologic lesions of the liver we feel justified in drawing a few general conclusions.

First, because of the extensive reserve and extensive reparative processes of the liver, symptoms of chronic hepatic disease appear as evidence that most of that organ has been destroyed and that the capacity for reparative processes is almost exhausted. In our experiments, however, removal of the agent responsible for the production of hepatic lesions has enabled the animal (and liver) to recover sufficiently to maintain fairly normal life.



FIG. 5. Loss of lobular arrangement of the liver and increased connective tissue in specimen shown in figure 4 ($\times 50$)

Second, a definite tendency toward intestinal hemorrhage is present in animals with extensively injured livers, and this tendency improves as the condition of the liver is allowed to improve, although the distended varices of the collateral circulation remain

Third, ascites in the experimental animal may be controlled by dietary measures

Fourth, diets rich in carbohydrates appear to be essential for the maintenance of animals with extensively injured livers

REFERENCES

- ¹BLAVER, M G Cholecystogastrostomy an experimental study, Arch Surg, 1929, xviii, 899-912
- ²BOILMAN, J L, and MANN, F C Studies on the physiology of the liver XVIII The effect of removal of the liver on the formation of ammonia, Am Jr Physiol, 1930, xcii, 92-106
- ³BOILMAN, J L, and MANN, F C Peptic ulcer in experimental obstructive jaundice, Arch Surg (In press)
- ⁴BOILMAN, J L, MANN, F C, and MAGATH, T B Studies on the physiology of the liver VIII Effect of total removal of the liver on the formation of urea, Am Jr Physiol, 1924, lxi, 371-392
XII Muscle glycogen following total removal of the liver, Am Jr Physiol, 1925, lxxiv, 238-248
X Uric acid following total removal of the liver, Am Jr Physiol, 1925, lxxvii, 629-646
XV Effect of total removal of the liver on deamination, Am Jr Physiol, 1926, lxxviii, 258-269
- ⁵LAMSON, P D, and RAYMOND, WING Early cirrhosis of the liver produced in dogs by carbon tetrachloride, Jr Pharmacol and Exper Therap, 1926, xxix, 191-202
- ⁶MAGATH, T B, and MANN, F C The effect of total removal of the liver in lower vertebrates, Am Jr Physiol, 1922, lxx, 486-487
- ⁷MANN, F C Studies on the physiology of the liver I Technic and general effects of removal, Am Jr Med Sc, 1921, clxi, 37-42
- ⁸MANN, F C, and BOILMAN, J L Liver function tests, Arch Path and Lab Med, 1926, i, 681-710
- ⁹MANN, F C, and BOOTHBY, W M Studies on the physiology of the liver XVI The respiratory quotient and basal metabolic rate following removal of the liver and injection, Am Jr Physiol, 1928, lxxxviii, 486-496
- ¹⁰MANN, F C, and MAGATH, T B The production of chronic liver insufficiency, Am Jr Physiol, 1922, lxx, 485
- ¹¹MANN, F C, and MAGATH, T B Studies on the physiology of the liver II The effect of the removal of the liver on the blood sugar level, Arch Int Med, 1922, xxx, 73-84
III The effect of administration of glucose in the condition following total extirpation of the liver, Arch Int Med, 1922, xxx, 171-181
IV The effect of total removal of the liver after pancreatectomy on the blood sugar level, Arch Int Med, 1923, xxxi, 797-806
VII The effect of insulin on the blood sugar following total and partial removal of the liver, Am Jr Physiol, 1923, lxxv, 403-417
- ¹²MANN, F C, BOILMAN, J L and MAGATH, T B Studies on the physiology of the liver IX The formation of bile pigment after total removal of the liver, Am Jr Physiol, 1924, lxxvi, 393-409
- ¹³MANN, F C, FISHBACK, F C, GAY, J G, and GREEN, J F Experimental pathology of the liver studies III IV and V Arch Path (In press)
- ¹⁴MANN, F C, SHIARD, CHARLES and BOILMAN, J L Studies on the physiology of the liver XI The extrapancreatic formation of bilirubin, Am Jr Physiol, 1925, lxxvii, 49-60

- ¹⁵MANN, F C., SHLARD, CHARLES, BOLLMAN, J L, and BALDES, E J Studies on the physiology of the liver XIII The liver as a site of bilirubin formation, *Am Jr Physiol*, 1926, lxxvii, 219-224
- ¹⁶MARKOWITZ, J, MANN, F C, and BOLLMAN, J L The glycogenic function of skeletal muscle in the dehepatized dog, with special reference to the rôle of insulin therein, *Am Jr Physiol*, 1929, lxxxvii, 566-583
- ¹⁷MINOT, ANN S, and CUTLER, JESSIE T Guanidine as a factor in the production of intoxication following liver injury, *Am Jr Physiol*, 1928, lxxxv, 396
- ¹⁸OPIC, E L, and ALFORD, L B The influence of diet on hepatic necrosis and toxicity of chloroform, *Jr Am Med Assoc*, 1914, lxii, 895-896
- ¹⁹RAVDIN, I S Some aspects of carbohydrate metabolism in hepatic disease *Jr Am Med Assoc*, 1929, xciii, 1193-1199
- ²⁰WILHELMJ, C M ; BOLLMAN, J L, and MANN, F C Studies on the physiology of the liver XVII The effect of removal of the liver on the specific dynamic action of amino acids administered intravenously, *Am Jr Physiol*, 1928, lxxxvii, 497-509
- ²¹WILLIAMSON, C S, and MANN, F. C Studies on the physiology of the liver V The hepatic factor in chloroform and phosphorus poisoning, *Am Jr Physiol*, 1923, lxxv, 267-276

Further Studies in Allergic Migraine:

Based On a Series of Two Hundred and Two Consecutive Cases*†

By RAY M. BALYEAT, M.A., M.D., F.A.C.P., and HERBERT J. RINKEL,
B.S., M.D. *Oklahoma City, Okla.*

IN a recent work on the hereditary factor in allergic diseases by one of us¹, it appears that migraine is interchangeable in the linkage with asthma and seasonal hay fever, which is excellent evidence that they have a common etiologic factor, namely, a specific sensitization. That protein sensitization is the causative factor in true bronchial asthma and seasonal hay fever is generally accepted. In a previous study² of allergic migraine a family history of allergy was elicited in 85.4 per cent of all cases. We observed that many asthmatic patients also suffered from migraine. A large per cent of migraine cases studied gave definite reactions to one or more foods and the results of treatment, based on our allergic findings, were equal to those obtained in the treatment of asthma. Our study led us to believe that the exciting factor in probably 100 per cent of true migraine cases is a specific sensitization to one or more foreign proteins.

The data contained in this paper were collected from a review of 202

consecutive cases of migraine examined at our private clinic, of which there were 135 female and 67 males, and from a careful questioning of 198 practicing physicians, 260 medical students, 107 nurses, 845 women teachers, 581 male and 521 female high school students, and 270 unemployed.

We were stimulated to give this subsequent review as we believe we have much additional evidence to substantiate the conclusions drawn from our first study.

AGL AI ONSLI

Alger³ finds 3 per cent of migraine cases develop before 10 years of age. Block⁴ states that the vast majority of cases develop symptoms before 25 years of age. Flatau⁵, in a history of 500 cases, shows that in 12 per cent the trouble started before the age of 15. Timme⁶ remarks that adolescence is the chief time of onset. Of our series of 202 cases, 60, or 29.7 per cent gave a definite history of onset of symptoms before they were 10 years of age. An additional 30.6 per cent manifested symptoms before 20. The fact that 60.3 per cent of all migraine develops before 20 is significant in our theory as to etiology, which will be discussed later is correct.

*Presented at the Baltimore Meeting of the American College of Physicians, March 27, 1931.

†From the University of Oklahoma Medical School and the Balyeat Hay Fever and Asthma Clinic, Oklahoma City, Okla.

TABLE I

Distribution of age at onset of clinical manifestation of migraine in patients of all ages, based on 202 cases

Age at Onset	No of Cases	Per Cent
First decade	60	29.7
Second decade	62	30.6
Third decade	50	24.7
Fourth decade	25	12.3
Fifth decade	3	1.4
After fifth decade	2	.9

In ascertaining the history of onset of migraine from adults many will answer the question as follows "As long as I can remember", or "About the time I started to school, as I remember the teacher would send me home from school on account of my headaches and vomiting" We are caring at present for a number of cases of migraine under 5 years of age, most of whom came not on account of the headaches but for relief of some other allergic syndrome We have a few cases whose symptoms did not appear until after 40 Organic brain lesion, however, should always be thought of in one developing headache at this age

INCIDENCE OF MIGRAINE

No reference has been found in the literature to the frequency with which this symptom complex occurs Business men, society women and students are reported to be more subject to the syndrome than other people That migraine is more common in women

than men is frequently mentioned As a means of trying to determine the number of people who suffer with typical attacks of migraine, we interviewed personally, or (with the assistance of Dr H H Cloudman, chief physician to the Oklahoma City Public Schools, through a detailed questionnaire) obtained data concerning the history of migraine in 2,728 individuals

It appears from the above findings that migraine is about twice as common in the female as in the male, and that it occurs twice as often in doctors and male high school students as in unemployed male laborers We have always contended that migraine, like other allergic diseases, occurs in those with a highly developed vegetative nervous system, therefore the percentage in the unemployed laborer should be much less, and according to our findings it is Considering the fact that the incidence of migraine is nearly 4 per cent in the indigent male labor-

TABLE II
Incidence of migraine in different classes of people

	Total No	No with Migraine	Per Cent
Physicians and medical students	101	31	29.9
Students	107	13	12.1
Unemployed male laborers	270	10	3.7
Women laborers	845	58	6.8
High school students, male	581	39	6.7
High school students, female	521	71	13.5

er, and about 10 per cent in the student and business class, a conservative estimate would place the percentage in people at large at about 7 per cent. Considering the age of onset and the disappearance of symptoms we estimate the number of people in the United States who now suffer from the syndrome at approximately 4,000,000.

From table II it can easily be seen that migraine is more common in business men, professional men, and teachers, than in other people. For example, we found that 79 per cent of all physicians and medical students gave a history of typical migraine, 104 per cent of all women teachers suffer from the disease, while less than 4 per cent of the indigent laboring men suffer from the symptom complex.

An answer to the question as to why migraine is more common among business men, professional men, and teachers, than in farmers, factory workers, and the indigent laboring class, is not easy. We wish to offer the following explanation as a possible answer. In a study of 1,217 patients with asthma and hay fever one of us¹ showed that the general health of allergic patients is far above the normal, and in the study of the mental activity of allergic children, we⁷ found 75 per cent were either in the superior, very superior, or genius class, which is far above the average. From our study of those who suffer from migraine it appears that they follow the rule of other allergic patients in regard to general health and also mental activity. One who has the ability to become specifically sensitive and suffer from some allergic condition has a highly developed vegetative nervous system.

Such a system is a prerequisite for a good business man, professional man, teacher, etc. The boy on the farm, or the one who comes from the laboring class, who inherits a highly developed vegetative nervous system, soon learns that he is a good student and enjoys his school work. He then becomes a university student. Therefore, from these children come our professors, doctors, lawyers, preachers, bankers, society women, etc. In other words they naturally drift into the part of society where they belong.

SYMPTOMATOLOGY

Not unlike asthma, the frequency of migraine headache varies greatly. Some patients suffer once a week, others every two or three weeks or every two or three months. The average frequency in our series is one attack in three weeks. Some patients are never entirely free from a slight headache between attacks. The duration of the attack again varies greatly, ranging from 12 to 96 hours. The average duration in our cases was 30 hours. In some instances a remarkable periodicity is noticed, especially in women who have attacks just before or during the menses. Again, like asthma, migraine may disappear during pregnancy.

Typical attacks of migraine consist of *First* a prodromal stage; *second* aura, *third*, attack, *fourth* post-migrainous symptoms.

The *prodromal stage* in our series was characterized by a period of depression with nervousness and irritability. In 26 per cent, 19 per cent stated that they felt unusually well the day previous to the attack, but were

noted in 23 per cent; and 53 per cent gave a history of a druggy or profound sleep the night preceding the headache.

The *aura* was manifested by faintness or vertigo in 21 per cent; scintillating scotomata in 81 per cent; hemianopsia in 22 per cent, and photophobia in 38 per cent. Auditory and olfactory symptoms were complained of by 4 per cent and 3 per cent respectively. Paresthesia of the hands occurred in 81 per cent; of the feet in 37 per cent; and of the face in 18 per cent. Motor symptoms were manifested by motor aphasia in 44 per cent, paresis in 0.6 per cent. Vasomotor disturbances were complained of in 7 per cent and mental confusion was reported or observed in 31 per cent.

The *attack* consisted of hemicrania at one time or another in 94 per cent of all cases studied, while the remaining 6 per cent never experienced pure hemicrania. A unilateral headache which became generalized was noted in 49 per cent. Nausea occurred in 73 per cent; emesis in 65 per cent. Pyrexia has been observed in some of the children during an attack.

Post-migrainous symptoms consisted of exhaustion in 40 per cent of our cases, polyuria in 6 per cent, rhinorrhea in 9 per cent, and a tendency toward sleepiness in 18 per cent.

We have observed a change from the typical migraine attack in a number of patients in the late 30's and early 40's. The headache became chronic, less severe, and usually generalized. The symptoms of the aural stage are usually less marked, nausea persists, but emesis is rare.

In children the headache may be severe, but is usually milder than

in adults. Gastric symptoms are much more common and severe in children than in adults. The so-called cyclic vomiting in children is probably migraine. Like asthma and other allergic symptom complexes, one may live under exactly the same environment, on a routine diet, and yet for some reason either lose his attacks entirely or have them milder for a period of years, only again to resume them in their original severity. Migraine frequently disappears in the late 40's in both men and women, but many continue to suffer throughout the 50's and early 60's.

THE HEREDITARY FACTOR IN MIGRAINE

That heredity is the most potent factor in the production of migraine is not questioned. Timme^a states that 50 per cent show this characteristic and that the mother transmits the disturbance in 75 per cent of the cases. Hassin^b says "heredity is most important in considering the cause of migraine. It may be direct (migraine in parents) or indirect (various other nervous or mental disorders in the family)." Both Timme and Hassin are neurologists and have studied the subject from a neurological standpoint. Neither mentions the possibility of a specific sensitization as an etiologic factor, or the relation that exists between migraine and the well established allergic syndromes. In studying many of the family trees in our series we have been impressed with the fact that the disease is interchangeable in the linkage with the well established allergic syndromes, namely, asthma, seasonal hay fever, perennial hay fever, urticaria.

and certain forms of eczema and colitis. It appears that it is only one of a number of syndromes which are metamorphosed in passing from parent to offspring. For example, five children in one family might be specifically sensitive to wheat. From such a sensitivity asthmatic symptoms might appear in the first child, eczema in the second, hay fever in the third, urticaria in the fourth, and migraine in the fifth. The mother of these five children might have been a hay fever sufferer due to the Russian thistle pollen and her mother have had asthma due entirely to a specific sensitivity to cat hair. The specific state is not inherited, but only the ability to become sensitive.

Four family trees are being offered to show the relation between migraine and the other allergic syndromes. In the pedigree shown in chart 1 you will note that the patient suffers from migraine and urticaria, that the father of this patient also suffered from migraine, but his sister had asthma, and the paternal grandmother had asthma, one of her sisters had asthma, and one brother suffered from asthma, but there is no record of migraine in her immediate family. The patient's son is also an asthmatic. In other words, in one generation asthma appears, in the next generation some of the children have asthma, others migraine, in the third generation migraine and urticaria, in the fourth, migraine only.

The family tree as shown in chart 2 is of interest as we find a patient with migraine, who has one brother and one sister with migraine, and whose mother had migraine. He has one son with hay fever and asthma. This son

has a newborn son. In all probability this newborn will not develop migraine, hay fever or asthma, but may develop a sensitivity to food and have eczema, urticaria or colitis.

In chart 3 we find a patient who suffers from epilepsy of a type that is definitely sensitive to food and has been controlled by food elimination. She has one sister with asthma and one with epilepsy. The sister with epilepsy has not been treated, but she has a child who has asthma. Our patient's grandmother had migraine, one maternal aunt had migraine, and one asthma. Her great grandmother had migraine and her great grandmother's sister had asthma. Here we find migraine transmitting epilepsy and in turn epilepsy transmitting asthma. Some of the neurologists have tried to show us that migraine is very closely associated with epilepsy. We have not found it so. We believe that those epileptics whose family history is saturated with migraine should be thoroughly studied from the standpoint of food sensitivity as a cause of their epilepsy.

Our patient as shown in chart 4 has migraine, asthma and eczema, and this is not an uncommon finding. He has a sister with asthma, his father had migraine, one paternal aunt with urticaria, one with migraine, and his paternal grandfather had asthma. The paternal grandmother had migraine and eczema. More than three-fourths of all migraine cases that we have studied suffer from other allergic diseases.

From the four cases presented and many similar ones we have studied it appears that migraine is interchangeable in the linkage with asthma, hay

fever, urticaria, and certain types of eczema, colitis and epilepsy. This observation, along with the clinical findings that 81.1 per cent of all of our cases suffer from other allergic syndromes is excellent evidence that the etiology is the same, namely, a specific sensitization to foreign protein.

Our patients and we inherit from the same germ plasma and therefore the same plans and specifications are used in our make up, which accounts for our having traits in common. We inherit only a hypersensitive cellular make up.

In some cases there seems to be a definite tendency to become sensitive to certain atopic groups, as has been pointed out by Coca⁸. Some patients apparently become sensitive to atopic substances in food with ease compared to other groups. Others develop a sensitivity to pollen with similar ease, others to animal dander, etc. The fact that a fair number of eczema, urticaria and migraine patients are comparatively negative to the inhalant group of atopic substances, both by testing and clinically, is striking. In other words, it appears that some patients may become allergic to one or more foods early in life and have eczema, urticaria or migraine, but never become sensitive, or if so to a sufficient degree, to the inhalant groups, in spite of the degree of contact, to develop asthma or hay fever. One of us⁹ has pointed out the fact that the massiveness of the contact dose has much to do with determining the atopic substance to which the patient will become sensitive.

We have also shown¹⁰ that a food sensitivity usually manifests itself in

the form of eczema, asthma or perennial hay fever rather early in life. We naturally would therefore expect migraine, if the etiology be that of a food sensitivity, likewise to appear at an early age, and from our findings it actually does.

In this series of cases a positive familial history of migraine or a family history of the well accepted allergic diseases, was elicited in 167, or 82.1 per cent. There were 145, or 71.3 per cent, with a unilateral family history and 23, or 11.4 per cent, with allergic histories on both sides of the family. Of those with a unilateral family history the trait was transmitted through the mother in 112 or 55.4 per cent and through the father in 57, or 28.2 per cent, of the cases. The figures relative to the transmission of the disease through the female do not correspond to those frequently quoted. Spain and Cooke¹¹ found a positive antecedent history in 58.4 per cent of a series of 462 cases of bronchial asthma and hay fever studied. Rowe¹² reported the occurrence of allergy in the antecedents in a series of bronchial asthma in 56.4 per cent. We¹³ reported a series of 1,000 cases of asthma and hay fever in which there was a positive antecedent history of allergy in 60.1 per cent, a series of 188 cases of urticaria with a family history of allergy in 67.6 per cent, and a series of 181 cases of eczema, in which a definite familial history of allergy was present in 64.3 per cent of the cases.

It appears from our findings previously given in this paper that an antecedent history of allergy is found in as great or a greater per cent of patients who suffer from migraine

than in those who suffer from asthma or hay fever. The fact that migraine is interchangeable in the linkage with asthma and hay fever and that there is a family history of allergy in as great or greater per cent of cases than in the well established syndromes leads us to believe that they have a common etiologic factor.

PREDISPOSING FACTORS

Like asthma, there are many conditions which play a part as predisposing factors. Consideration should be given the following:

- (1) Physical fatigue,
- (2) Mental fatigue and depressed states,
- (3) Thyroid dysfunction,
- (4) Genito-sexual,
- (5) Toxic states,
- (6) Disturbance of the special senses

Typical attacks of migraine may follow exhaustive physical exertion, prolonged worry, extreme depression, or, in women, occur just previous to or at the menstrual period. Endogenous toxins, such as from infected teeth, tonsils, or toxins from an exogenous source, such as partially burned gas fumes, may bring on headache. Refractive errors, or a disturbance of the normal hearing, smelling, seeing or tasting may play a part in precipitating an attack. The various factors just mentioned must be considered not as basic ones but predisposing only. In many of our cases after the food to which they were specifically sensitive was removed from the diet they remained free from their usual migrainous attacks. In part of the menstrual cycle, the physical fatigue, thyroid

dysfunction, toxic state, or disturbance of the special senses, as the case might be. We are inclined to believe that the stress and strain of life as a predisposing factor has been very much overestimated, since 29.7 per cent of our cases had typical migraine before 10 years of age and an additional 30.6 per cent before 20. In these cases the stress and strain of life surely had little to do with their symptoms.

ETIOLOGY

Over a century ago it was suggested by some French investigators that migraine, asthma, hay fever, eczema, urticaria, and epilepsy, might be of similar origin. In 1890 and again in 1900 Haig¹⁴ wrote rather extensively concerning migraine, in which he felt that an increase in uric acid was the chief cause. The disease received but little investigation until the last decade. Pagniez¹⁵ in 1920 treated the syndrome by the use of peptone on the assumption that it was anaphylactic in origin. Ball¹⁶ reported a series of 20 cases treated with peptone and states that clinically migraine is associated with asthma, hay fever, urticaria, epilepsy and therefore he believes that it is due to a hypersensitiveness to food. In 1927 Vaughan¹⁷ studied 33 cases from an allergic standpoint. This seems to be the first series of migraine cases to be carefully tested for a food sensitivity and their treatment based on such findings. Vaughan was the first to show that patients sensitive to food or foods could be partially or wholly relieved by specific avoidance, and that an attack of headache could be produced by the ingestion of the specific food. Later in the same year Row mentions four patients with migraine

who obtained great relief on diets based on the elimination of the foods to which he found them sensitive. In 1928 Rowe¹⁹ states that food allergy must be considered a possible cause of all cases of migraine. In 1930 one of us² reported a series of 55 cases studied from the standpoint of protein sensitization. Treatment of these cases consisted of eliminative measures based on positive food findings. The cases were studied primarily for the purpose of determining the exciting factor or factors. It was concluded from this small series that the exciting factor in probably all cases is a specific sensitivity to one or more food proteins. Recently Eyermann²⁰ has reported a study of 63 cases in which he showed that many cases could be freed from their headaches by elimination of the foods to which they are sensitive, and then headaches could be produced by deliberate partaking of the specific food. Recently in reviewing the histories of 100 cases of asthma in the adult we found that 20, or 20 per cent, had associated with their asthma typical migraine. In other words, it appears that the symptom complex is more common in allergic than in nonallergic people. Beckman²¹ has suggested a disturbance of the acid-base balance as an etiologic factor in allergic diseases. R and S Weissmann-Netter²² found the hydrogen ion concentration and alkali reserve normal in the migraine patient in periods of freedom from attacks but a tendency for alkalosis to develop 48 hours prior to an attack. It is believed by many that carbohydrates have much to do with precipitating an attack. Zinsser²³ states that carbohydrates are non-antigenic sub-

stances, therefore they could not be the exciting factor but might act as a predisposing factor.

The present series of 202 cases under consideration includes the 55 previously reported. In our study of the last 147 cases the intradermal method of testing for food sensitivity has been employed much more extensively. In every case studied a reaction to one or more proteins was found. We use the scratch method of testing routinely but this is always followed routinely by the use of the intradermal method. It has been our experience that a large percentage of the foods do not react to the scratch test and the intradermal method therefore is necessary to find all food factors. If a question arose as to a reaction being of a nonspecific origin passive transfer was employed. Of the cases studied, 70, or 34.2 per cent, suffered from asthma, 98, or 48.5 per cent, had hay fever, 41, or 20.3 per cent, had eczema, 35, or 17.3 per cent, had urticaria, and 14, or 6.9 per cent, had colitis. In the series we naturally found many sensitive to the inhalant group of atopic substances. During the last year all cases have been tested with allergens made in our own laboratories, which have been tested clinically for potency. Any food or any combination of foods, may cause migraine, but the following foods, as etiologic factors, are of importance in order as they are numbered.

- (1) Milk,
- (2) Wheat,
- (3) Eggs,
- (4) Nuts.
- (5) Beans.
- (6) Fish.

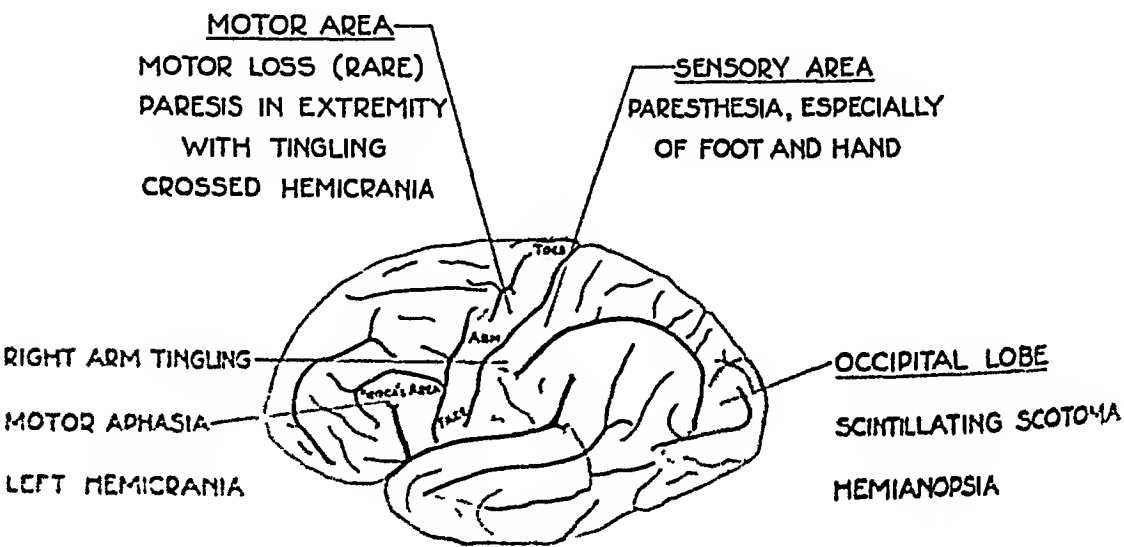
Multiple sensitization to food is very much the rule. Frequently, however, one food may be of primary importance clinically. We have learned that a one plus reaction to a particular food may be much more important than a four plus reaction to some other food.

PATHOLOGY

Little has been written on the pathology of migraine. Church and Peterson²⁴ remark, "In the absence of any known morbid changes we must fall back on theories and analogies."

An acceptable theory of migrainous pathology must take into consideration the frequency in early life, the influence of the vegetative nervous system, and the frequently recurring condition which leaves no permanent organic change that may be demonstrated in histologic study. Endarteritis is not an acceptable theory because approximately 60 per cent of the migraine patients will suffer before the second

decade. Further, the pathologic theory must explain the multiple cortical manifestations; namely, scintillating scotomata, hemianopsia, paresthesias, motor aphasia, paresis and occasionally auditory or olfactory aura. One patient presents the following symptoms in order named: paresthesia of the right finger, progressing up to the shoulder, then scintillating scotomata, followed by hemianopsia, motor aphasia, mental confusion, with the headache on the left side, and with subsequent nausea and vomiting. The headache may become generalized, or remain localized, or pass down into the upper cervical region. What is the most likely histopathogenesis of these symptoms? It seems somewhat improbable for this to be due to vasospasm. The isolated and definite areas affected do not correspond to the arterial supply of the cortex. Rackemann²⁵ states that the possibility of cerebral vascular spasm, as shown by Cobb and his associates,



CEREBRAL LOCALIZATION OF COMMON MIGRAINE SYMPTOMS

Migraine localized areas of vasomotor dilatation seem to explain best the symptoms observed and reported by those who suffer from migraine.

makes it proper to consider migraine on a pathological as well as on a clinical basis as related to other allergic manifestations. With the vasomotor spasm theory we cannot agree. We believe that there is ample evidence to classify migraine as allergic, and therefore we see no reason why one should consider the pathology of migraine as differing from the typical pathological lesion of other allergic diseases, namely, local edema. In urticaria we have a lesion characterized by primary dilatation of the blood vessels of the cutis, followed by an exudation of fluid into the tissues with cellular infiltration. Hansel²⁰ has described in detail the allergic reaction of the nasal mucosa. In all of these allergic manifestations there is a marked pathogenic similarity. In view of this fact, why should we consider that the allergic reaction within the cortex is different histopathologically from other allergic reactions? It is reasonable to assume that the attack is due to a sudden dilatation of the vessels of the cerebral cortex instead of a spasm. The fact that about 15 per cent of the patients can obtain freedom from their headaches by the use of epinephrin or ephedrine is evidence in favor of this theory. Until more convincing evidence is presented we see no reason to assume that the allergic pathogenesis differs in migraine from any of the other allergic diseases.

The question naturally arises as to why the local dilatation of the vessels of the cerebral cortex of the brain should occur, and not in other structures of the body. It appears that the French experimenter Arthus²⁷, may have explained this phenomenon. He observed that the mechanism of

anaphylaxis, for example, in the rabbit differed from that of the guinea pig, but only in the site of the reaction. In the rabbit, the site of the occurrence of the reaction is in the muscle of the arteriole of the lung. The arterioles are constricted completely so no more blood can pass through. The blood pressure falls completely and the animal dies. In the guinea pig the site of the reaction is in the muscle of the bronchiole. In the dog the site of this reaction is in the liver. Thus, the site of the anaphylactic reaction due to the same foreign protein in one animal might be in the muscle of the bronchiole, in another in the muscle of the arteriole of the lung and in the third, in the liver. Anaphylactic and allergic reactions are not the same, but similar in many respects. Clinically one patient may be sensitive to wheat and have asthma due entirely to the sensitization to that specific food, another have no symptoms of asthma whatsoever but have hives, the third patient manifest symptoms of perennial hay fever due to a wheat sensitivity and the fourth patient local symptoms in the brain, namely, migraine due entirely to a sensitivity to wheat. In other words, a sensitivity to the same food may manifest itself in producing edema of the mucous membrane of the bronchial tree in one individual, giant urticaria in another, a congestion of the nose in the third and in the fourth a local edema in some part of the brain. From a study of experimental anaphylaxis in the animal and clinical manifestations of allergy in the human it seems logical to believe that the migraine patient has a localized edema of the brain due to a specific sensitization

to food in a similar way to that in which urticaria cases have localized edema of the skin, or asthmatics have localized edema of the bronchial *cul de sac*. After the local edema of the bronchial tubes, a hive on the skin, or a patch of eczema disappears, the area involved will show no structural changes. Likewise in an autopsy on a patient who has suffered from severe migraine for a number of years, no pathological changes can be detected.

DIAGNOSIS OF MIGRAINE

The direct diagnosis of migraine is based upon a history of familial headaches and in the majority of the cases a history of other allergic manifestations either in the antecedent who has the sick headaches or his blood relatives. It is aided by the history of other allergic manifestations in the individual and the direct history of paroxysmal recurrent sick headaches that started early in life, and manifested by a chain of symptoms which in the typical case is characterized by four stages—the prodromal, the aura, the attack, and the post-migrainous phase. During the prodromal stage the patient is either depressed or hyperactive and many note bulimia or a druggish sleep. Following the prodromal state the patient may develop the typical headache without preceding aura. Sensory symptoms are the rule. The most common sensory symptoms are scintillating scotomata, photophobia, hemianopsia (usually homonymous), and paresthesia of the hands, feet or face. The majority of these sensory symptoms are contralateral to the hemicrania. Motor symptoms occur in approximately 50 per cent of

the patients, motor aphasia being the most common.

In a small percentage of the patients there may be mental confusion. Vasomotor symptoms are fairly common and may occur before the headache appears or during its course. In some cases there is flushing, in others pallor, or there may be general profuse perspiration. Occasionally we note inequality of pupils.

The headache, on third stage, develops as a rule along with some of the sensory or motor aura, but as stated above may develop without any preceding sensory or motor symptoms. It varies in degree and location but in the great majority of the patients it is a hemicrania, and in approximately 50 per cent of the patients it starts as a hemicrania and becomes generalized. At one attack the headache may be a pure hemicrania and in a subsequent attack start as a unilateral headache and become generalized. Along with the headache the patient usually develops nausea, which may or may not be followed by emesis. As a rule emesis is more common in the early years of the headache.

The duration of the attack may extend from a few hours to several days, may alternate from side to side, and as the headache wears off the patient passes into the post-migrainous stage characterized by exhaustion, sleepiness, polyuria, or nasal irritation.

The direct diagnosis of migraine is established when relief is obtained by removing specific foods from the diet and symptoms recur on deliberate partaking of these foods. It is preferable that these foods be removed and added without the patient's knowledge.

Physical findings are more valuable to rule out the presence of other conditions than to establish the direct diagnosis. The laboratory findings in the typical case will be of little value in confirming the diagnosis of migraine. Testing by the scratch and intradermal methods will reveal positive reactions to various foods or other foreign proteins in practically 100 per cent of the cases.

DIFFERENTIAL DIAGNOSIS

All cases of migraine are cases of headache, but not all cases of headache are migraine. The syndrome must be differentiated from functional headache, trifacial neuralgia, myalgia intoxications, such as those of alcohol, tobacco and uremia, and from headache due to a brain tumor or pituitary dysfunction. As a means of differentiating migraine from pituitary headache Engelbach²⁸ states

"The diagnosis of pituitary headache, however, cannot be made upon the characteristic location, severity of pain and associated ocular or gastric symptoms. There must be sufficient other evidence of pituitary disorder, such as osseous, genital, dermal or pigmentary changes, accompanying these headaches to warrant such a diagnosis."

Tierney²⁹ states

"our cases of pituitary headache have been more often found in individuals with other signs of pituitary disturbance, have been bilateral, nonparoxysmal, associated with different ocular manifestations, if any, and not usually accompanied by nausea and vomiting"

Migraine associated with vomiting is not uncommon. More than one patient with migraine has lost his normal appendix due to a mistaken diagnosis. A clear cut history of periodic headache occurring since childhood or young

adult life, with perfect freedom between attacks, especially if there is an ancestral history of allergy, spells migraine. A differential diagnosis of cases in which the headache is of recent origin is more difficult. The average physician probably would not think of migraine as a diagnosis in a child coming with a complaint of periodic headache. In all probability the child would be sent to the oculist or rhinologist for investigation. Even the pediatrician frequently forgets that migraine is common in childhood.

About 50 per cent of our cases developed migraine before 15 years of age. About 7 per cent of all people have migraine sometime in life. In other words, at least 2 per cent of all children during the first decade suffer from migraine. In making a differential diagnosis a family history of allergic conditions should be given much weight. One should be careful of making a diagnosis of migraine however, in one whose symptoms appear after 40 years of age unless the family tree is filled with allergy. Migraine, like other allergic diseases, is not always typical. In an atypical case with a family history filled with allergy one would probably not err in making a diagnosis of migraine. On the other hand, if the symptoms are not clear cut and there is no definite family history of allergy, one is not justified in making such a diagnosis.

PROGNOSIS

'Timme' states that with few exceptions migraine disappears in the fourth or fifth decade. From our study this appears not to be exactly true since of the 202 cases 22 came

seeking relief during the sixth decade. From the standpoint of life and death prognosis is good. Many patients also have other allergic diseases. It is not uncommon for a patient to have his life seriously interfered with due either to the frequency, or to the severity, of migrainous attacks. Of our cases, 4, or 19 per cent, were not able to carry on a gainful occupation on account of the severity of the attacks, and in 10, or 49 per cent of our patients, their symptoms seriously interfered with their work.

TREATMENT

Treatment should consist of *first*, pre-marital advice, *second*, thorough elimination of predisposing factors; *third*, careful investigation and elimination of the exciting factors; and *fourth*, treatment of the attacks.

Pre-marital Advice It is certainly the duty of a family physician or specialist dealing with migraine to instruct the parents of allergic children concerning the possibility of the transmission of the disease. A young man with migraine who marries a girl with migraine or some other allergic syndrome, or one whose family tree is saturated with allergy, may expect some form of allergy to appear in about three-fourths of his children.

Predisposing Factors Until the last decade much attention was given to the predisposing factors as little was known about the exciting ones. Predisposing factors should be determined and eliminated. For example, plenty of rest and sleep should be taken by the sufferer, avoidance of physical exhaustion and mental fatigue and worry is always in order. Toxic states should be investigated and eliminated if

found. Correction of refractive errors and any error of the special senses should be done.

When all the foregoing measures have been taken many patients will be some better but not until the exciting factors, namely, the foods to which they are sensitive, are found and removed, can one hope for good results.

Elimination of Exciting Factors In our present series of 202 cases, who have been treated by specific food eliminative measures, 44, or 21.7 per cent, received either total, or more than 80 per cent, relief, which we consider excellent results. Another 76, or 37.6 per cent, received between 60 and 80 per cent relief, which we count good results, and another 58, or 28.7 per cent, received from 40 to 60 per cent relief, which we consider fair results. Twenty-four cases had but little or no relief.

From our findings it appears that the results in the treatment of migraine are as good or better than those obtained in nearly any other chronic disease. The average patient who receives more than 80 per cent relief, practically speaking, is well, as the symptoms interfere little with his comfort, the comfort of his family, or his ability to carry on a gainful occupation. Frequently those who receive more than 60 per cent relief are extremely grateful because they realize that their unhappy, uncomfortable, impractical condition has been greatly changed. Diet manipulation based on specific sensitization to food findings seems logical, is practical, and there is no element of danger in it.

Treatment of the Attack For those cases who have prodromal symptoms

appearing the day before the actual attack, manifesting themselves by irritability, nervousness, abnormal appetite, etc., carbohydrates and sugars should be restricted in the diet, a saline cathartic should be given, and but little or no evening meal should be taken. The following morning if the attack actually appears, no breakfast should be taken, and if the stomach will permit, a second mild saline cathartic should be given. The noon lunch should be a light one. Sugars and carbohydrates should be restricted. Some sufferers feel better lying down without too much light in the room.

As many remedies as there are drugs in the Pharmacopeia have been suggested for the relief of pain during the attack and in only an occasional attack do they really do much good. Morphine and codeine should be used as the last resort. Barborka³⁰ has suggested the use of the ketogenic diet. With such a method the patient is kept in a state of ketosis. From an allergic standpoint such a diet in some cases should relieve the patient from symptoms, or partially relieve him, as there would be removed either entirely or in part the foods to which he is specifically sensitive. To keep a patient in a state of ketosis for a chronic disease like migraine seems rather severe, as there is surely an element of danger. An eliminative diet based on a study of the foods to which the patient is specifically sensitive on the whole gives results equal to those of practically any other chronic disease.

CONCLUSIONS

1. Migraine appears to be common in childhood since nearly one-third of

all cases studied developed symptoms during the first decade.

2. The syndrome is more common in business men, professional men and teachers, than in laborers.

3. About seven per cent of all people in the United States sometime in life suffer from the symptom complex.

4. Like asthma, symptoms of migraine in childhood may vary greatly from those of the adult. Gastric symptoms are usually marked.

5. Migraine is interchangeable in the linkage with other allergic syndromes.

6. A family history of allergic diseases was elicited in 167 out of 202 cases, or 82.1 per cent.

7. Of the 202 cases studied 81.1 per cent suffered from other allergic syndromes.

8. From our findings it was concluded that the exciting factor in all cases of migraine is a specific sensitization.

9. There are many predisposing factors which should be investigated and eliminated.

10. The pathology in migraine is probably a local vasomotor dilatation producing a local congestion of the brain corresponding to a hive on the skin.

11. A familial history of allergy or a history of allergic manifestations in one who suffers from headache and but does not establish a diagnosis of migraine.

12. The treatment of migraine based on allergic findings gives results equal to the treatment of practically any other chronic disease.

REFERENCES

- ¹BALYEAT, RAY M The hereditary factor in allergic diseases with special reference to the general health and mental activity of allergic patients, *Am Jr Med Sc*, 1928, clxxvi, 332
- ²BALYEAT, RAY M Allergic migraine based on the study of fifty-five cases, *Am Jr. Med Sci*, 1930, clxxx, 212
ALGER Quoted by E Bates Block in *Tice's Practice of Medicine*
- ³BLOCK, E BATES *Tice's Practice of Medicine*
- ⁴FLATAU. Quoted by Geo Boris Hassin in *Abt's Pediatrics*
- ⁵TIMME, WALTER *Oxford System of Medicine*, p 654a
- ⁶BALYEAT, RAY M The general health and mental activity of allergic children, *Am Jr. Dis of Child*, 1929, xxxvii, 1193-1197
- ⁷COCA, ARTHUR F Studies in hypersensitiveness, XXIX On the influence of heredity in atopy, *Jr Lab and Clin Med*, 1927, xii, 1135-1139
- ⁸BALYAT, RAY M Acquisition of specific hypersensitiveness based on the study of one thousand asthma and hay fever cases, *South Med Jr* 1928, xxi, 554-559
- ⁹BALYEAT, RAY M Asthma in children, *Jr Okla St Med Assoc*, 1927
- ¹⁰SPAIN, W C, and COOK, R A Studies in specific hypersensitiveness, *Jr Immunol*, 1924, ix, 523
- ¹¹ROWE, ALBERT H The treatment of bronchial asthma, *Jr Am Med Assoc* 1925, lxxvii, 1902-1905
- BALYAT, RAY M Urticaria—diagnosis and treatment based on the study of one hundred and eighty-eight cases, *Jr Okla St Med Assoc*, 1913 xxiv
Allergic eczema—based on the study of one hundred and eight-one cases, *Jr Allergy*, 1930, i, 516-528
Allergic diseases their diagnosis and treatment, 3d Ed, 1930 F A Davis Co. Philadelphia p 200
- ELSON, ALEXANDER Uric acid as a factor in the causation of disease, 5th Ed 1900, P. Blakiston's Son & Co, Philadelphia
- ¹²PAGNIEZ, P On the cause of migraine *Presse méd* 1920, xxviii, 253
- ¹³BALL, FRED E Migraine its treatment with peptone and its familial relation to sensitization diseases, *Am Jr Med Sci*, 1927, clxxiii, 781
- ¹⁴VAUGHAN, WARREN T Allergic migraine, *Jr Am Med Assoc*, 1927, lxxviii, 1383-1386
- ¹⁵ROWE, ALBERT H Allergy in the etiology of disease, *Jr Lab and Clin Med*, 1927, xiii, 31-40
- ¹⁶ROWE, ALBERT H Allergy its manifestations, diagnosis and treatment, *Jr Am Med Assoc*, 1928, xci, 1623-1629
- ¹⁷EYERMANN, CHARLES H Allergic headache, *Jr Allergy*, 1931, ii, 106-112
- ¹⁸BECKMAN, HARRY A Treatment in general practice, 1930, W B Saunders Company, Philadelphia
- ¹⁹WEISSMANN-NETTER, R and WEISSMANN-NETTER, S Equilibre acide-base et migraine, *Compt rend Soc de biol*, 1925, xcii, 341-343
- ²⁰ZINSSER, HANS Foreword in Rackemann's *Clinical Allergy*, 1931, Macmillan Co, New York
- ²¹CHURCH, ARCHIBALD and PITLSON, FREDERICK Nervous and mental diseases, 1922, W B Saunders Company, Philadelphia
- ²²RACKEMANN, FRANCIS M *Clinical allergy*, 1931, Macmillan Co, New York
- ²³HANSEL, FRENCH K Clinical and histopathologic studies of the nose and sinuses in allergy, *Jr Allergy*, 1929, i, 43-70
- ²⁴ARTHUS, M Injections repetées de serum de cheval chez le lapin, *Compt rend Soc de biol*, 1903, iv, 817
- ²⁵ENGELBACH, WM Pituitary tumor, *Med Clinics of N Am*, 1924 vii, 1365
- ²⁶TIERNEY, JOHN I Headache, *Med Clinics of N Am*, 1924 vii, 1515
- ²⁷BARBORKA, CLIFFORD J Migraine review of treatment by ketogenic diet in five cases, *Jr Am Med Assoc*, 1910 vi, 1825-1828

Diet As a Factor in the Etiology of Anemia*†

By RICHARD A. KIRN M.D., Philadelphia, Pennsylvania

JUST as the body strives to preserve a constant composition of other important factors in the internal environment so, too, the red cell and hemoglobin content of the blood is maintained at a normal level even under very adverse circumstances. When human beings^{1,2,3} or animals⁴ are subjected to prolonged and complete fasting, red cell and hemoglobin figures per unit volume remain at or near normal until long after marked general body wasting has taken place. In partial starvation, when food intake is below body needs, anemia does not occur until very late, provided the diet is reasonably diverse. For example, a hysterical woman, observed in the University Hospital, had in the course of 14 months starved herself to an extreme degree of emaciation yet her blood showed 4,760,000 red cells and 78 per cent of hemoglobin. This is due in part to the careful hoarding and re-utilization of available material (as we know to be the case with blood pigment, and as is perhaps the case with cell stroma), and in part to the fact that the materials necessary for red cell and hemoglobin formation are abundantly present in a great variety

and number of foods. So anemia is uncommon in the rapid wasting of Grave's disease or severe diabetes (The average red cell count in 100 cases of Grave's disease was 4,610,000, and the hemoglobin, 80 per cent. One patient lost 105 pounds in 12 weeks yet his blood showed 4,600,000 red cells and hemoglobin 90 per cent.) It is safe to say that anemia results from dietary causes only when the diet is greatly restricted as to certain foods and then only when such a diet has been persisted in for a long time.

Much has been learned in recent years of the rôle of diet in blood formation. Especially the studies of Whipple, of Minot, and of their collaborators have demonstrated the quantitative effects of individual foods on red cell and hemoglobin production in various pathologic states. In the light of their findings we are better enabled not only to treat anemic conditions but also to evaluate diet as a factor in their production.

DIET AND SECONDARY ANEMIA

Diet plays its most conspicuous part in the production of secondary anemia. The essential feature is usually a diet poor in iron and other hemoglobin building foods. While anemia from this cause may occur at any age, there are certain times of life when it is more common. The condition first pre-

*Read before the Baltimore Meeting of the American College of Physicians, March 27, 1931.

†From the Medical Division of the Hospital of the University of Pennsylvania.

sents itself, and with great frequency, in infancy. The normal infant born at term possesses a sufficient store of hemoglobin and iron to tide it over the lactation period until a more varied diet meets current blood-building needs. Should the infant have a deficient supply to begin with, or should the inception of mixed feeding be too long deferred, a hypochromic or secondary anemia will result. Pediatricians have, therefore, long recognized that nutritional anemia is most likely to develop in premature infants, in those underweight at birth, in twins, in those whose lactation period is too prolonged or who early develop abnormal eating habits. Abnormalities of gastrointestinal function can further add to the infant's troubles by interfering with absorption. Mackay⁵, on the basis of observations in 770 infants, concludes that the condition is essentially an iron deficiency which is curable by iron medication (iron and ammonium citrate) and preventable by the same means if treatment is started at the age of two months. She finds no evidence of a vitamin deficiency. Hill⁶ reaches similar conclusions but obtained quicker results by combining liver with iron therapy.

Adolescence is the next period in which we often see anemias due to a diet low in iron and in other hemoglobin building foods. Chlorosis is the most marked example of this group, and while other factors are possibly concerned in its etiology, one cannot help but feel that the virtual disappearance of this condition in the last few decades is largely due to the better knowledge of diet and exercise in adolescence. In its place, however,

there are seen an increasing number of chloro-anemias in middle age, chiefly in women, due to a diet low in iron, in meats and vegetables, high in carbohydrates, and aptly called by Minot the "Soda Lunch Diet." To recognize the true nature of these cases clinicians should investigate with greater care than heretofore the diet habits of their patients and, in order to advise them intelligently, should familiarize themselves with the rôle of diet factors in hemoglobin construction as so thoroughly worked out by Whipple and his collaborators^{7,8}.

Lack of vitamins has been suggested as a possible cause of anemia. Here the evidence is as yet meager and contradictory. Experimentally, Happ⁹ found that rats kept for a long period on a diet low in anti-rachitic substance became anemic. Secondary anemia was observed by Sartori¹⁰ in pigeons deprived of vitamin B and in guinea pigs on a diet low in vitamin C, and a pernicious type of anemia by Wills and Mehta¹¹ in rats on diets with no vitamin C and almost no vitamin A. On the other hand, no effects on red cells or hemoglobin were noted by Sherif and Baum¹² in rats deprived of vitamins A, B, C and D, or by Cartland and Koch¹³ in rats deprived of vitamins A, B, and E; or by Sure, Kirk and Walker¹⁴ in vitamin B or E deficiency in rats. Clinically, Koessler and Maurer¹⁵ have claimed that 75 per cent of patients with severe anemia give a dietary history of vitamin deficiency, and Aron¹⁶ calls attention to the fact that anemia in children is often associated with scurvy. However, Keefler and Yang¹⁷ and Pillat and Yang¹⁸ in observations on anemia as

ciated with various clinical avitaminoses point out that in the majority of instances the diets of these individuals have been deficient in hemoglobin-building substances as well. It is conceivable, however, that an associated avitaminosis could aggravate the anemia-producing effect of a diet also deficient in red cell and hemoglobin-building materials.

The claim that a copper deficiency may play a part in causing secondary anemia has not been substantiated. Whereas Waddell, Steenbock and Hart¹⁹ found that of 13 metals copper alone, when added to iron, cured anemia in young rats caused by a whole milk diet, Drabkin and Waggoner²⁰ cured such animals by a synthetic diet containing less copper than the original milk diet.

Brief mention is made of a form of nutritional anemia that has attracted considerable attention especially in Germany in recent years. In 1916, Scheltzema^{20a}, and in 1918, Schwenke²¹ independently reported cases of anemia in infants fed on goat's milk and since then numerous similar observations have been recorded. The blood picture is usually that of secondary anemia, but in a considerable minority of cases there is present an anemia pseudo-leukemica^{22,23} with severe anemia, high color index, macrocytosis, nucleated red cells, leukocytosis, pallor and an enlarged spleen, and which Stoeltzner²² refers to as possibly an infantile form of pernicious anemia. The cause of the anemia is not certain. Brouwer²⁴ points out that it is probably not an iron deficiency, for the anemia develops at an age before the infant normally exhausts its iron store. While goat's

milk has been found quite low in vitamin C^{25,26}, the addition of vitamins to the diet is not effective²⁷, and puppies fed on goat's cream and cow's skimmed milk become anemic²⁸. It is, therefore, probably not an avitaminosis. The myelotoxic action of certain fatty acids abundantly present² offers perhaps the best explanation. An unknown constitutional factor has also been invoked²⁹. A change to cow's milk diet is curative.

DIET AND PERNICIOUS ANEMIA

Since Biermer³⁰ in 1872 in his original communication on progressive pernicious anemia expressed the opinion that insufficient and unsuitable food was a factor in its etiology, much has been written of the possible relation of diet to this disease. However, not until the announcement by Minot and Murphy³¹ of the treatment by liver feeding was any real progress made in this direction.

As a basis for the discussion of the relation of diet to pernicious anemia attention is called to the hypothesis of etiology which has been proposed by Castle, Townsend and Heath³² as a result of their excellent studies on the nature of the reaction between normal human gastric juice and beef muscle in producing a substance that leads to clinical improvement in pernicious anemia, similar to the effect of liver feeding. Briefly stated, the interaction of an *intrinsic factor* (an as yet unidentified substance secreted by the normal gastric mucosa and not present in patients with pernicious anemia) and an *extrinsic factor* (in the diet probably protein in nature—e.g., beef muscle—or closely related) results in a

substance (or substances) which after absorption produces a marked hematopoietic effect in pernicious anemia. *Pernicious anemia is essentially due to the lack of the intrinsic factor*. The substance resulting from the interaction of the intrinsic and extrinsic factors exists preformed in liver and certain other foods, by the feeding of which, pernicious anemia may be successfully treated.

How may diet be related to this hypothesis?

1 In the first place, Castle, Townsend and Heath³² suggest that abnormal diets may possibly have a relationship to the original gastric dysfunction in pernicious anemics. This is as yet hypothetical.

2 In the second place, there are probably a great many more *potential* pernicious anemics than those who have actually developed the disease: individuals with probably a partial or possibly even complete loss of the intrinsic gastric factor; individuals who nevertheless have not become anemic because in their diets they manage to obtain enough of the *preformed* hematopoietic substance (liver, kidney, others?) to meet their needs. The well-known familial occurrence of achylia gastrica and pernicious anemia lends support to this view. In such individuals the deprivation of certain foods might be the means of precipitating or hastening the anemia. In Germany the period of greatest food lack as a result of the war and the financial crash was the year 1923. Protein food was particularly scarce. In that year Germany recorded its highest incidence of pernicious anemia. In 1926 the incidence was about the number of

pernicious anemia patients in 1923 was seven times as great as in 1908, and three times the number in 1926^{16,33,34} when the stringency had been largely relieved. Then again, in such potential anemics a diet which has just sufficed at a given age may become inadequate in later years, for Minot³⁵ has observed that, while an average of 300 grams of liver was an adequate daily maintenance dose for pernicious anemia patients at the age of 45, those at 60 required 600 grams and at 69 well over 600 grams, probably because of diminished absorption or utilization, incident to arteriosclerosis.

3 To the above I wish to add another possibility: namely, that in rare instances an Addisonian type of blood picture may result in a patient whose diet is deficient in the *extrinsic factor*. I wish to report a patient who in the presence of free hydrochloric acid in the gastric juice, developed an Addisonian blood picture, an anemia apparently brought on by an unusual type and degree of prolonged voluntary diet restriction and in which a more liberal diet produced a typical remission. The data available are unfortunately rather scant but perhaps not wholly inadequate.

CASE REPORT

Case I. T. O., an Irishman of 50 years was admitted to the University Hospital on Sept. 20, 1921, with chief complaints of weakness, swelling of the legs and dimness of vision. At the age of 33 he had become a vegetarian in the ordinary sense of the word, using milk and eggs freely in the diet. After some years, however, he became convinced that this was inconsistent, and he added milk and eggs. He then proceeded to distinguish between fine and gross vegetables, the latter being those for which he had no use. These were used as food for his

specified, among others, peas and beans) and these in turn he decided to use very sparingly. For these and other reasons he became estranged from his wife and thereafter lived alone in an apartment where he prepared his own food. He worked long hours as a teacher and magazine writer, and eating was only of minor significance in his scheme of things. For example, he would boil a huge pot full of potatoes and spinach on Sunday and would eat these cold the rest of the week, together with plenty of fruits, raw vegetables, bread and nuts. In the past six years there had been gradually increasing distress after meals, failing vision, diminishing appetite and an increasing constipation. In the past year these symptoms had become aggravated and in addition there had developed weakness, swelling of the feet and ankles, dyspnea on exertion, and, more recently, numbness and tingling in the feet. His weight had fallen from a maximum of 125 pounds to 115. He did not complain of a sore tongue.

Physical examination showed a pale pasty-looking individual with markedly swollen legs. There was no jaundice of skin or sclerae. The tongue was smooth and pale. The spleen was not palpable. Knee jerks and Achilles jerks were preserved but diminished. Vibratory sense was unfortunately not tested. An eye examination showed optic atrophy, a central color scotoma, marked contraction of the retinal arteries, vision 3/60—(in 1916 it had been 6/6 according to the ophthalmologist's record). During the first two weeks in the hospital the temperature rose as high as 100.4° F., thereafter it remained normal. The urine had a specific gravity of 1.010, contained no sugar and no albumin, the urinary sediment showed occasional hyaline casts, no blood or pus. The feces contained no occult blood.

The blood figures are shown in table I and chart 1.

The blood picture with its high color index, red cell changes and leukopenia suggested a pernicious anemia. In view of his serious condition a transfusion was decided upon. The patient, however, refused to accept blood unless it were from another vegetarian and one who did not use to-

baecol. Iron was ordered, but unfortunately in the form of "ovoferrin", which the patient refused because of the "ovo". He did receive several hypodermics of iron and arsenic but finally refused them because of discomfort at the site of injection. He thereafter received no medication. Because it was felt that his anemia had been caused by his bad diet habits, it was decided to feed him white meat of chicken, milk, and eggs. This had to be done surreptitiously by disguising these foods in various combinations with vegetables. There resulted a marked and rapid improvement in the patient's general condition as well as in the blood picture. His vision improved to the extent that he could again read with the aid of a hand lens. The edema, obviously due to protein starvation, promptly disappeared, while his weight increased to 120 pounds. On Jan 7, 1922, the patient left the hospital and returned to his work.

For several months he continued in fair health. But he returned to his original diet habits and eventually began to fail again. A gastric analysis made in March, 1922, showed a total acidity of 30 and a free hydrochloric acid of 18. In April, 1922, the blood count had again fallen to 1,400,000 and the hemoglobin to 35 per cent. He was urged to return to the hospital, but he refused, going instead to a vegetarian sanitarium in another city where he died a few weeks later.

In the light of present knowledge it seemed to me that this was a case in which an Addisonian type of blood picture had resulted from a diet so restricted as to be insufficient in the *intrinsic factor* necessary for interaction with normal gastric juice to produce the substance which stimulates hemopoiesis in pernicious anemia, a case in which the feeding of a diet adequate in animal protein produced a characteristic remission.

I therefore reviewed the case histories of all anemic patients that had been in the University Hospital with particular reference to their dietary

habits. These included 183 cases of pernicious anemia, 164 cases of secondary anemia and 25 cases of chlorosis. Of the chlorotics, 6 gave a history of poor dietary habits preceding the onset of anemia, but none of a degree that could be interpreted as possibly deficient in the sense of case I. In none of the secondary anemia cases was a marked diet deficiency noted. In two cases diagnosed as pernicious anemia the evidence was suggestive.

CASE REPORT

Case II. R. G., a Porto Rican woman of 55, was admitted to the University Hospital on Oct. 15, 1929, with a chief complaint of weakness. After the death of her husband 4 years before, she had become worried and depressed. For the past 3 years she had eaten no meat, practically no vegetables, and had limited her food largely to white bread, milk and coffee. She gradually became weaker and her weight fell from 156 to 136 pounds. She did not have any paresthesias. There were periods of looseness of the bowels. The past history included an attack of filariasis ten years before.

Physical examination showed some pigmentation of the skin. The tongue was smooth and atrophic. Vibratory sense was not tested "because of linguistic difficulties." Reflexes were not mentioned. The spleen was not enlarged. There was some edema of the legs. The urine was not abnormal. The

van den Bergh test gave a negative direct reaction and an indirect reading of 0.65 unit. Fragility of the red cells was within normal limits. A fractional gastric analysis showed a maximum figure of 68 for total acidity and of 34 for free hydrochloric acid.

The blood findings are given in table II.

The blood picture was that of Addisonian anemia, and the feeding of liver extract produced a typical remission. The patient left the hospital on Oct. 31, 1929, and has not been heard from since then. During her stay in the hospital she had no diarrhea but rather a moderate constipation.

Case III. T. B., a white man, aged 75, was admitted to the University Hospital on April 30, 1925, with a chief complaint of weakness and swelling of the legs. Ten years before he had been sent to the penitentiary where he had been until the day of admission. Nine years ago he had begun to have attacks of indigestion with epigastric distress and belching of gas and sour material. He then restricted his diet, avoiding all meat, beans and potatoes. The indigestion attacks became less frequent but did not cease, so he further restricted his food in quantity and quality. In the past year he had become weaker, emaciated and obviously anemic with more recently edema of the legs and increasing constipation. He was finally sent to the hospital because of suspected gastric cancer.

Physical examination showed an emaciated old man weighing 98 pounds. There was a slight yellow tinge of the skin. The superficial arteries were sclerotic. The tongue was not described. The heart was normal.

TABLE II
Blood Findings in Case II

Date	RBC	Hb %	Color Index	WBC	Neut	Lymph	Mon	Eos	Platelets	Remarks
10/14/29	2,900,000	65	1.12	3,600	31	65	2	2		Some red blood cells and polymorphonuclear cells present since admission.
10/19	Liver extract one vial 11 d									
10/22	4,000,000	84	1.05	3,200						
10/23	3,600,000	81	1.26	4,000						
10/25	3,800,000	85	1.25	5,100	53	41	1	2		WBC's 53, 41, 1, 2. Neutrophils 53, 41, 1, 2. Lymphocytes 41, 41, 1, 2. Monocytes 1, 1, 1, 2. Eosinophils 2, 2, 1, 2. Platelets 2, 2, 1, 2.

and the pulse rate normal The spleen was not palpable and the peripheral reflexes were normal The blood pressure was normal There was moderate edema of feet and legs The urine contained no sugar and no albumin, and the urinary sediment was negative save for occasional hyaline casts A complete gastrointestinal x-ray study was negative Fractional gastric analysis showed a maximum of 98 total acidity and 53 free hydrochloric acid The van den Bergh test gave a negative direct reaction and an indirect reading of "a trace" There was some increased fragility of the red cells, hemolysis beginning at 0.5 and being complete at 0.375 The blood counts are given in table III

in vitamins, especially in vitamins B and C In both of these patients, therefore, it must be admitted that the anemia was due, in part at least, to these factors In case I, however, the diet covered a considerable range of vegetable foods, and many of these in the raw state, so that it seems unlikely that the diet was to any great degree deficient in any vitamins or in hemoglobin-building foods An intelligent and educated person,—he was a Doctor of Philosophy—the patient

TABLE III
Blood Findings in Case III

Date	R B C	Hb %	Color Index	W B C	Neut	Lymph	Mono	Eosin	Remarks
5/1/25	2,880,000	65	1.14	8,250	53	40	6	1	"No reticulocytes"
5/17	2,750,000	50	0.91	4,800					
5/23	2,800,000	65	1.16	7,600	40	50	6	4	

The diagnosis, which the attending physician recorded as pernicious anemia, while made apparently by a process of exclusion, has little to support it in the data at hand No description of the blood smears are found in the record No treatment was given and his condition at the time of discharge was unimproved His subsequent fate could not be learned

The blood findings in cases II and III are graphically shown in chart 2

In the light of case I, meager though the data are, it is suggested that in rare instances an addisonian blood picture may result from a diet so unusually restricted, especially in animal protein, as to be deficient in the *extrinsic factor* necessary for erythropoiesis

Two objections must, however, be considered In the first place, to what extent was the diet of these patients deficient in other respects? Certainly in case II, and probably in case III, the diet was deficient in iron, as well as

well knew the need of diversification in diet, and this he conscientiously sought to achieve within the limits of his convictions Protein lack would appear to be the outstanding, and perhaps the only defect in this patient's diet

Then there is lacking a further important proof namely, that the gastric juice in these cases actually did contain the *intrinsic factor* The presence in all three of these patients of free hydrochloric acid in the stomach contents may be suggestive but is of course no proof of the presence of the intrinsic factor Castle, Townsend and Heath³² have observed two cases of pernicious anemia with free hydrochloric acid in the gastric juice, which juice was nevertheless ineffective on incubation with beef muscle. But the fact that in case I the feeding of chicken muscle, milk and egg (foods which do not contain the erythro-

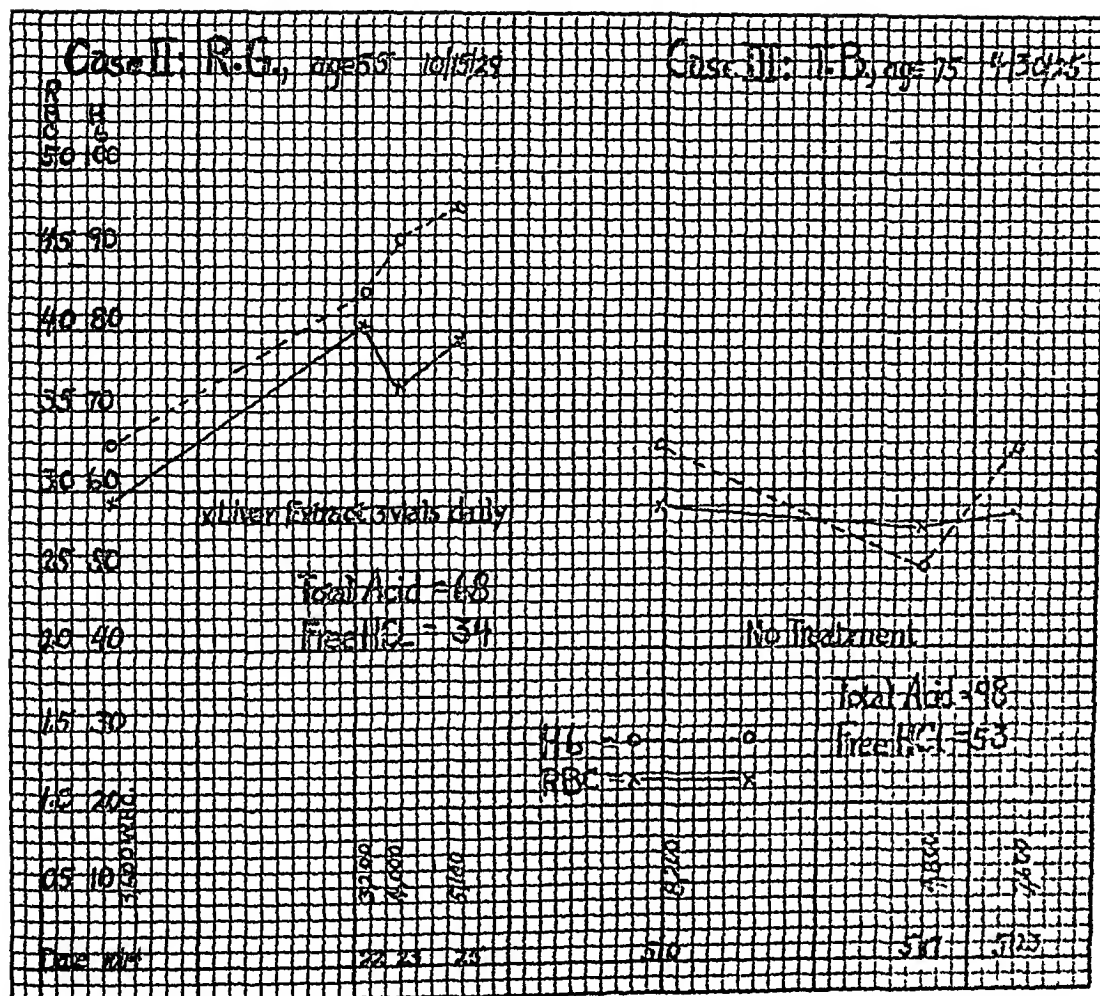


CHART 2

poietic stimulant in a preformed state) produced a typical remission, at least suggests the presence of the *intrinsic factor* in that patient's gastric juice.

The production of an Addisonian blood picture in the manner suggested must be exceedingly rare. So Willson and Evans²⁶ in their series of 111 cases of pernicious anemia noted no significantly abnormal eating habits. A search of the literature has failed to reveal a case quite comparable with that of our first patient. O'Hara and Greval²⁷ reported typical pernicious anemia in a boy of 14 who had lived

largely on bread, milk, potatoes, and candy. Here there may well have been an avitaminosis, as well as iron deficiency. Furthermore the patient had a true achylia. Avitaminosis undoubtedly also played a part in Acknowledged patient, a woman of 39 with edema, and a suggestive blood picture following six months' subsistence on bread, molasses, tea and occasional little salted meat and with history of beriberi 15 years before. The case of Hindu women with pernicious anemia reported by Wills and Edgerton²⁸ is

in animal protein, were also low in vitamins A to C, to which deficiency the authors attribute the anemia. In short, it would seem to occur only in a "super-vegetarian", such as was our patient.

SUMMARY

1 Anemia from dietary causes results only when an unbalanced diet has been persisted in for a long time.

2 The usual result of such an unbalanced diet is a secondary type of anemia, a chloroanemia.

3 The diet fault in these cases is (a) most commonly a lack of iron and hemoglobin-building elements, (b) rarely perhaps a lack of one or more vitamins, or a combination of (a) and (b).

4 The development of pernicious anemia may perhaps be hastened by diet restrictions (probably of certain animal proteins) in those with achylia gastrica (partial or complete lack of intrinsic factor for stimulating erythropoiesis).

5 The combination of avitaminosis, low protein and iron intake may possibly at times produce an Addisonian blood picture (case II, III?).

6 In rare instances an Addisonian blood picture may result from a diet inadequate, through prolonged protein starvation, in the extrinsic factor, which is necessary for the formation of the substance for stimulating erythropoiesis (case I).

REFERENCES

- ¹LABBE, M., STREVENIN, H., and NEPVEUX, F. A voluntary fast, *Bull et mém Soc méd d hôp. de Par*, 1922, xlv, 975.
- ²SISON, A. G. Clinical observations on experimental starvation in human beings, *Philippine Jr Sci*, 1920, xvii, 415.
- BERRI, P., and WEINBERGER, M. Formed elements of human blood during prolonged fasting, *Hæmatologica*, 1927, viii, 407.
- ³KANDA, Y. I. Pathology of starvation, *Mitt a d Med Fak d k Univ zu Tokyo*, 1922, xxix, 131.
- ⁴MACKAY, HELEN M. M. Nutritional anemia in infancy—a common deficiency disease (iron therapy), *Proc Roy Soc Med (Sect Dis Child)*, 1929, xxii, 29.
- ⁵HILL, K. W. Nutritional anemia in infancy—deficiency disease, *New Eng Jr Med*, 1929, cci, 261.
- ⁶WHIPPLE, G. H. Hemoglobin construction within the body as influenced by diet factors, *Am Jr Med Sci*, 1928, clxxv, 721.
- ⁷ROBSCHT-ROBBINS, F. S., and WHIPPLE, C. H. Blood regeneration in severe anemia—influence of spinach, cabbage, onion and orange juice, *Am Jr Physiol*, 1930, xcii, 400.
- ⁸HAPP, W. M. Anemia in rats on deficient diets, *Bull J Hopk Hosp*, 1922, xxxiii, 163.
- ⁹SARTORI, C. Modifications in blood of fasting pigeons and guinea pigs under vitamin deficiency and on reduced diet, *Pathologica*, 1928, xx, 288.
- ¹⁰WILLS, L., and MEHTA, M. M. Production of pernicious anemia (*Bartonella* anemia) in rats by deficiency diet, *Brit Med Jr*, 1930, i, 1167.
- ¹¹SHIRIR, S., and BAUM, H. Thrombocytes and red blood picture in avitaminotic diseases, *Arch f Kinderh*, 1927, lxxx, 269.
- ¹²CARILAND, G. F., and KOCH, F. C. Diet proteins and vitamins as related to hemoglobin production in rats, *Am Jr Physiol*, 1928, xvii, 249.
- ¹³SURE, B., KIRK, M. C., and WALKER, D. J. Effect of avitaminosis on hematopoietic function, *Jr Biol Chem*, 1929, lxxxiii, 375, 387, 401.
- ¹⁴KOESSLER, K. K., and MAURER, S. Treatment of pernicious anemia with a diet

- rich in vitamins, *Jr Am Med Assoc*, 1927, lxxxix, 768
- ¹ARON, H Alimentary factor in anemia in children and adults, *Deutsch med Wchnschr*, 1927, lxx, 1125
 - ¹⁷KLEFFER, C S, and YANG, C S The rôle of the various vitamins in the production of anemia, *Nat Med Jr, China*, 1929, xv, 419
 - ¹⁸PILLAR, A, and YANG, C S The blood picture in keratomalacia in adults, *Arch Ophth*, 1930, iv, 309
 - ¹⁹WADDELL, J, STEENBOCK, H, and HART, E B Specificity of copper as a supplement to iron in cure of nutritional anemia, *Jr Biol Chem*, 1929, lxxxiv, 115
 - ²⁰DRABKIN, D L, and WAGGONER, C S Hemoglobin maintenance and production upon synthetic diets, etc, *Jr Biol Chem*, 1930, lxxxix, 51
 - ²¹SCHIEFFEMA, G Goat's milk as infants' food, *Nederl Maandschr v Verlosk*, 1916, v, 407
 - ²²SCHWINKER, JOHANNA Severe anemias in early childhood, *Jahrb f Kinderh*, 1918, lxxxviii, 181
 - ²³STOELTZNER, W Anemia from use of goat's milk *Munch med Wchnschr*, 1922, lxxix, 4
 - ²⁴BARBACCI, P Pathological effects of vitamin deficiencies in goat's milk, *Riv di clin pediat*, 1928, xxvi, 489
 - ²⁵BROUWER, E Anemia from goat's milk in infant feeding, *Jahrb f Kinderh*, 1923, cii, 257, 357, ciii, 51
 - ²⁶NASSAU, E, and POGORSCHETSKY, H Vitamin content of goat's milk, *Deutsch med Wchnschr*, 1925, li, 985
 - ²⁷GIANZMAN, E Clinical and experimental studies on goat's milk anemia and dystrophy, *Jahrb f Kinderh*, 1926, cxii, 127
 - ²⁸KIRSH-HORRIG, E, and KIRSCH O Goat's milk anemia in infants *Wien klin Wchnschr*, 1924, lxxvii, 568
 - ²⁹BEUMER H and WIECZORFKE, G Experimental study of pathogenesis of goat's milk anemia, *Jahrb f Kinderh* 1924, cxii, 311
 - ³⁰BRUNING, H, and FISCHER, W Goat's milk anemia in infants, *Med Klinik* 1925, xxi, 12
 - ³¹BIERMILR, A Über progressive perniciose Anämie, *Korr bl f Schweiz Ärzte* 1872, ii, 14
 - ³²MINOT, G R, and MURPHY, W P Treatment of pernicious anemia by a special diet, *Jr Am Med Assoc*, 1926, lxxviii, 470
 - ³³CASTLE, W B, TOWNSEND, W C, and HATH, C W Observations on the etiologic relationship of achylia gastrica to pernicious anemia, *Am Jr Med Sci* 1930 cxliii, 305
 - ³⁴BIRTHORF, A Undernutrition and diseases, especially atypical forms of pernicious anemia, *Munch med Wchnschr*, 1923, lxx, 419
 - ³⁵CURSCHMANN, H *Munch med Wchnschr*, 1923, lxx, 1370
 - ³⁶Personal communication
 - ³⁷WILSON, C P and FARRIS, F A Analysis of clinical histories of patients with pernicious anemia in Johns Hopkins Hospital from 1918 to 1922 inclusive, *Bull J Hopk Hosp* 1924, lxxv, 38
 - ³⁸O'HARA D and GREGG J S An unusual case of pernicious anemia *Boston Med and Surg Jr* 1929, cxcvii, 129
 - ³⁹WILSON W R Future of anemia *Brit Med Jr*, 1930 ii, 217
 - ⁴⁰WILLIS J and TAYLOR S A Peric anemia of pregnancy survey of dietary and hygienic conditions of women in Bombay *Indian Jr Med Res* 1929, xliii, 283

Anemia Associated With Gastrointestinal Disorders: Clinical Considerations and the Value of Iron in Treatment*†

By CHESTER S. KEEFER, M.D. F.A.C.P. Boston, Mass.

THE relationship between disorders of the gastrointestinal tract and anemia is of considerable importance because it is common, and in some instances the anemia resembles that seen in pernicious anemia. The conditions attracting most attention have been achylia gastrica, sprue, *Dibothriocephalus latus* infestation, multiple intestinal strictures, gastrectomy, hookworm infestation, and the chronic diarrheas. In the past, it has been customary to attribute the anemia to "toxic factors" and most of the cases have been studied from that point of view. In recent years, with the discovery of liver as a potent factor in the treatment of pernicious anemia¹ many of these conditions have been reinvestigated in an attempt to gather more precise information regarding the various factors responsible for the anemia and to evaluate the various therapeutic agents which are most beneficial.

At this time, twenty patients with

anemia associated with chronic dysentery, seven patients with anemia associated with hookworm infestation, and four patients with anemia associated with tuberculosis of the intestine are discussed. No attempt will be made to deal with the question of the relationship between disturbances in gastric function and anemia except to point out that since the recent important work of Castle and his associates² in pernicious anemia, the relationship of faulty gastric function to other forms of anemia is becoming better appreciated. The observation of Strauss³ in the anemias of pregnancy and Mettier and Minot⁴ and Waugh⁵ in chlorotic types of anemia indicate that disorders of gastric function may be of importance in some anemias other than pernicious anemia. However, before final conclusions can be drawn regarding the precise relationship between achylia gastrica and anemias, further observations are necessary.

ANEMIAS ASSOCIATED WITH CHRONIC DYSENTERY

Twenty patients with chronic dysentery and anemia have been studied. The diagnosis of dysentery was made

*Presented at the Baltimore Meeting of the American College of Physicians, March 27, 1931.

†From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital, and the Department of Medicine, Harvard University.

from the clinical picture, culturing the organisms from the stools and finding the characteristic ulcers in the sigmoid on direct examination. All were due to bacillary infection. In the group as a whole all of the features which are characteristic of pernicious anemia were observed. There was atrophy of the papillae of the tongue in nine, gastric anacidity in four, combined system disease in two, retinal hemorrhages in two, and the blood picture of pernicious anemia in five. Other interesting clinical features were the presence of conditions associated with food deficiency in the form of edema disease in six, peripheral neuritis in two, hyperkeratosis follicularis in two, keratomalacia in two and pellagra in one.

Etiology of Anemia In considering the various factors responsible for the anemia, the duration of the diarrhea, the character of the diet, the changes in gastric secretion, the presence or absence of intestinal hemorrhage, and infection were analyzed.

In all of the twenty cases, the diarrhea had been present for two months or longer. It was evident, however, from the study of a number of other patients with chronic dysentery that factors besides the duration of the diarrhea were of importance in producing an anemia because only about twenty per cent of all patients with chronic dysentery develop an anemia. As a result of this observation it was necessary to study the question further in order to determine why anemia was present in some and not in others. As many patients with diarrhea had restricted their food intake and since this increased the nutritional disturbance

the diets of the patients with anemia were investigated with care. It was evident that eighteen of the twenty patients had been on diets which were inadequate both in quantity and quality and it was noteworthy that the two patients who had not definitely restricted their diets had a gastric anacidity. From these observations it was concluded that anemia was more common in the patients with a chronic diarrhea and a restricted diet than in those who had a chronic diarrhea and a normal diet. On the other hand, if in the presence of a continuous diarrhea the diet were not restricted this did not necessarily protect the patient from anemia if gastric anacidity were present. But since gastric anacidity was present in only three of the patients with anemia, it was clear that it was not responsible for the anemia in the group as a whole. In one patient the secretion of acid was only temporarily disturbed, in the other two the anacidity was permanent.

A factor of importance in enhancing the anemia was blood loss. In all of the patients, a few red blood cells were present in the stools. In none of the patients, however, was there a history of a large hemorrhage and none was observed. Furthermore the anemia improved in spite of continued slight loss of blood when the proper therapy was employed. It appeared, therefore, that blood loss was only a contributory and not the essential factor in producing the anemia.

The relative importance of the enteric infection in the case of bacterial intoxication was difficult to evaluate. As the anemia did not develop in all patients with chronic

entery, and since the anemia improved following various forms of treatment in spite of the persisting dysentery, it is unlikely that infection was of importance as a direct cause but operated indirectly because it caused an ulcerative colitis and diarrhea which interfered with nutrition

From these observations it is concluded that the anemia associated with

stances secreted by the worms, or to infection following the intestinal lesions produced by the worms. There is another factor of importance in any consideration of the etiology of the anemia, namely, malnutrition. In this study, seven patients with hookworm infestation and anemia were observed who recovered from their anemia without the removal of the worms. This

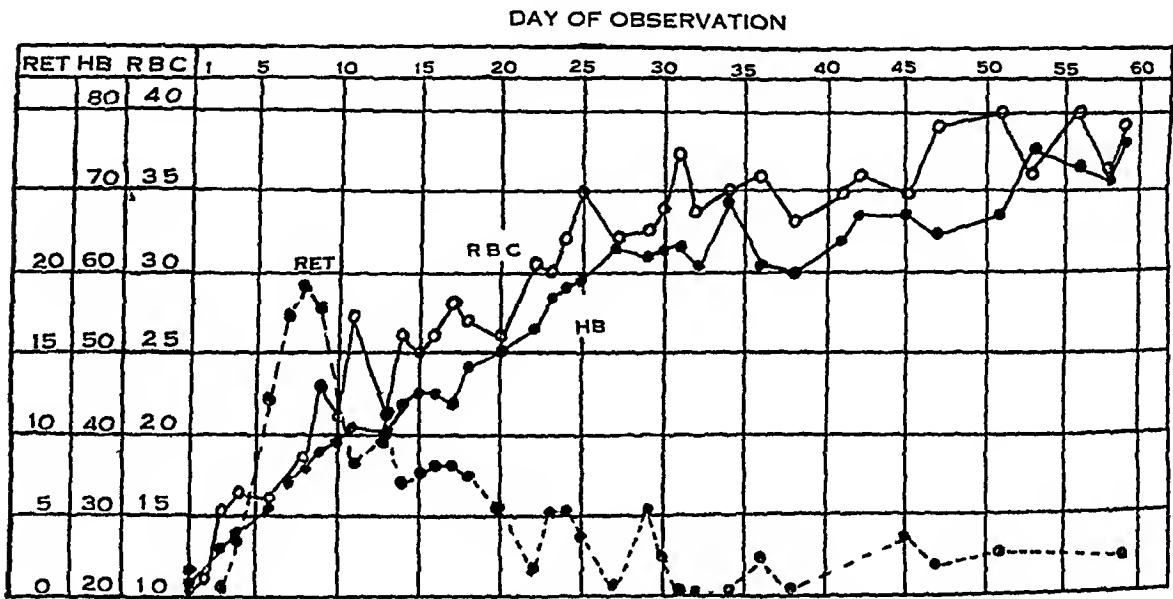


CHART I Patient with anemia associated with chronic dysentery recovering following an adequate amount of food

chronic dysentery results from nutritional disturbances which are due to chronic diarrhea and inadequate diets. The part contributed by blood loss, disturbances in gastric function, and infection are not essential. Chart I illustrates the response of the blood in a patient following an adequate diet.

ANEMIA ASSOCIATED WITH
HOOKWORM INFESTATION

The cause of the anemia associated with hookworm infestation remains obscure. In the past, it has been customary to attribute the anemia to chronic blood loss, hemolytic sub-

stances secreted by the worms, or to infection following the intestinal lesions produced by the worms. There is another factor of importance in any consideration of the etiology of the anemia, namely, malnutrition. Such an explanation is extremely unlikely and it is well known that although the majority of patients with hookworm infestation and anemia have heavy infestations, there are striking exceptions in which

anemia is present with a few worms, and conversely no anemia may be present with many worms. In view of these observations, factors other than the worm burden must be considered in explaining the anemia that is associated with hookworm infestation. Darling, Barker, and Hacker⁶ called attention to malaria and malnutrition as factors in explaining the severity of some cases and, more recently, Shapiro⁷ has discussed the discrepancy between the degree of anemia and the worm burden in two groups of patients with hookworm infestation, and emphasized the importance of nutritional factors in influencing the development of anemia. From a study of the literature and these seven cases, there appears to be no question but that Shapiro's observations are correct. It is necessary, therefore, to study factors other than the worm burden in any investigation of the anemia of hookworm disease.

The recent observations of Wells⁸ require comment. By direct observation, he has shown that the hookworms attached to the intestine of dogs withdraw blood from the intestine and eject it into the lumen in such a way that it is lost. He suggests that this blood loss is responsible in part at least for the anemia observed in hookworm infestation.

It has been generally recognized that blood loss is of importance in contributing to the anemia in many of these patients and it probably plays a part in many. In the patients whose blood returns to normal following adequate therapy for anemia, in spite of the fact that they continued to carry the worms, there must be other conditions respon-

sible for the anemia. It is likely, therefore, that while chronic blood loss is responsible for a part of the anemia in some of these patients such factors as malnutrition are of greater importance.

Chart 2 illustrates the response of a patient with anemia associated with hookworm infestation recovering following the feeding of liver and iron while he continued to carry the worms.

ANEMIA ASSOCIATED WITH TUBERCULOSIS OF THE INTESTINE

Tuberculosis of the intestine of the ulcerative type is frequently associated with anemia. Observations have been made on four patients with diarrhea resulting from tuberculous enteritis. In all there was an anemia and evidence of malnutrition and deficiency disease. In order to gather more information regarding the influence of nutritional disturbances in producing the anemia apart from the restrictions of the diet, the records of forty-two patients with tuberculosis of the intestines proven at necropsy were studied. The results of this study have been recorded in detail elsewhere⁹. It was found that the patients with ulceration of the intestine with diarrhea, or alternating constipation and diarrhea, were the ones who developed anemia most frequently whereas if the intestinal function was not definitely disturbed throughout the course of the illness anemia occurred no more often than in fatal cases of pulmonary tuberculosis without intestinal ulceration or in cases of hyperplastic cecal tuberculosis. It appears, therefore, that the presence of diarrhea is an important factor that can lead to

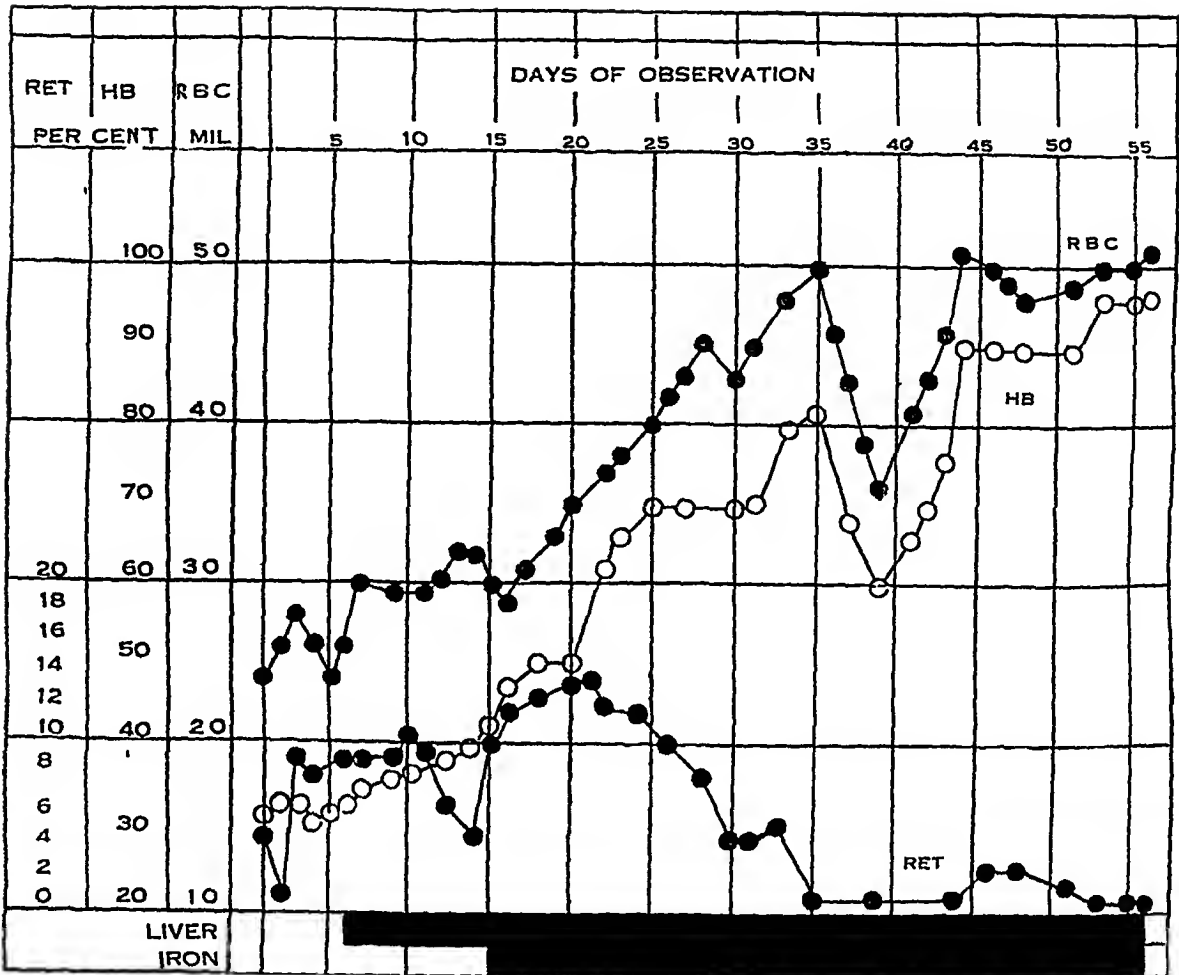


CHART 2 Patient with anemia associated with hookworm infestation recovering from the anemia following the feeding of liver and iron while he continued to carry the worms

TABLE I
Blood Findings in Patients With Tuberculosis of Intestines

Case Number	Red Blood Cells in Millions Per cu mm		Hemoglobin Per Cent		Reticulocytes Per Cent		Remarks
	Treatment		Treatment		Treatment		
	Before	After	Before	After	Before	After	
1	1 39	1 70	29	38	3 3	14 4	Keratomalacia Edema
2	3 08	4 22	58	81*	6	2 2	
3	3 33	3 24	52	48	0	3 6	Edema disease
4	2 76	3 33	28	42	6	4	

*Improvement due to blood transfusion

the development of anemia in these patients Table 1 summarizes the blood findings of the four patients who were studied

Chart 3 illustrates the course of the blood following treatment in a patient with chronic diarrhea due to tuberculosis of the intestines

The occurrence of the various food deficiency disorders in the patients studied is of interest in supporting the thesis that the anemia was largely the result of nutritional disturbances Keratomalacia, beriberi, edema disease, and hyperkeratosis follicularis were attributed to vitamin A deficiency, beriberi to a lack of vitamin B (G),

and edema disease to protein starvation

In the interpretation of clinical features attributed to specific nutritional defects, it is essential to bear in mind that single food deficiencies seldom exist in man In order that single food deficiencies may be studied in animals the diets must be selected with meticulous care When deficiency disorders exist in man, there is no such selection of food for the diet so that it is usually defective in a number of substances This is apparent in any study of nutritional disturbances in man It is not surprising, then, to find multiple nutritional defects in the same indi-

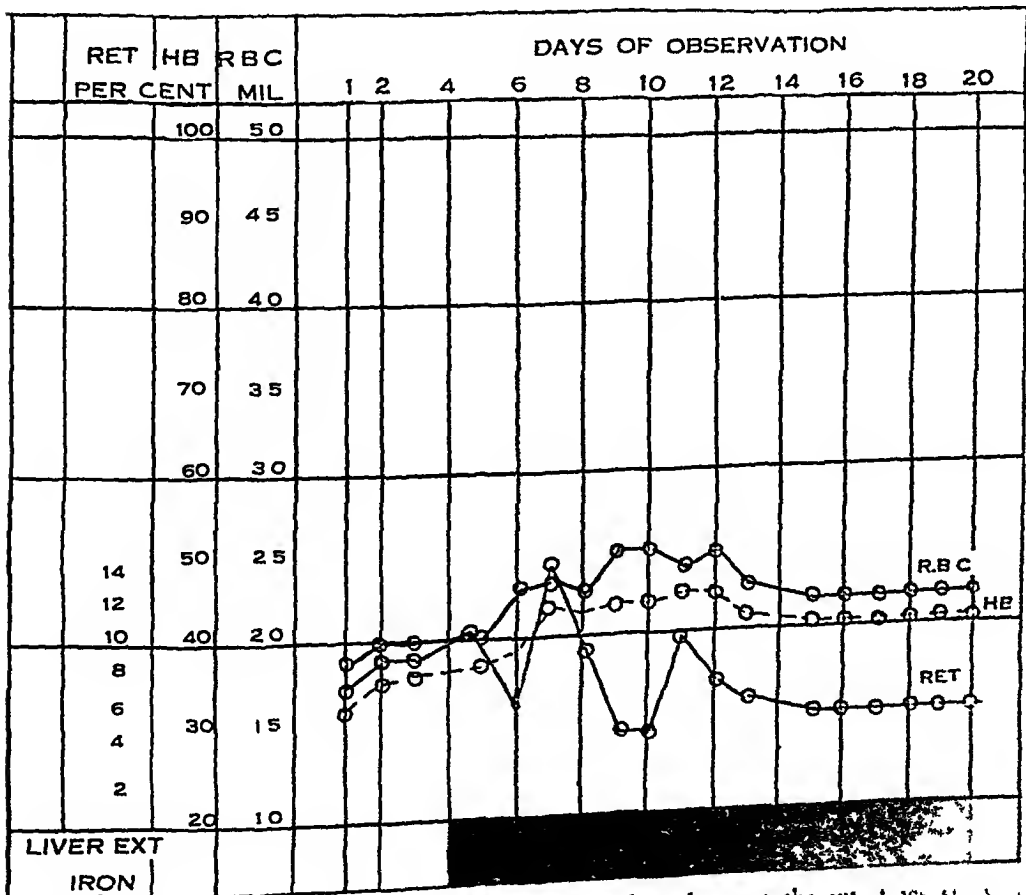


CHART 3 Patient with anemia associated with tuberculosis of the intestines. No improvement following the feeding of liver extract and iron

vidual, and it is such observations that make the precise interpretation of anemia so difficult. As an example of these difficulties, it may be recalled that any or all of the deficiency disorders due to avitaminosis may be present without anemia, so that when anemia is present under these circumstances, its exact cause is difficult to determine with certainty. In spite of this fact, it is well established that anemia does result from a lack of certain substances in the diet and recently Mettier, Minot, and Townsend¹⁰ have shown that vitamin C stimulates blood regeneration in

patients who have anemia associated with scurvy.

The response of the reticulocytes to liver or iron therapy in the cases discussed here has been compared with their response in a series of cases when the anemia undoubtedly resulted from faulty diets. In chart 4 the reticulocyte counts at the peak of the rise have been plotted against the total number of red cells at the beginning of treatment. It is manifest from the chart that the reticulocytes promptly increased following therapy for anemia in all groups and as a rule the lower

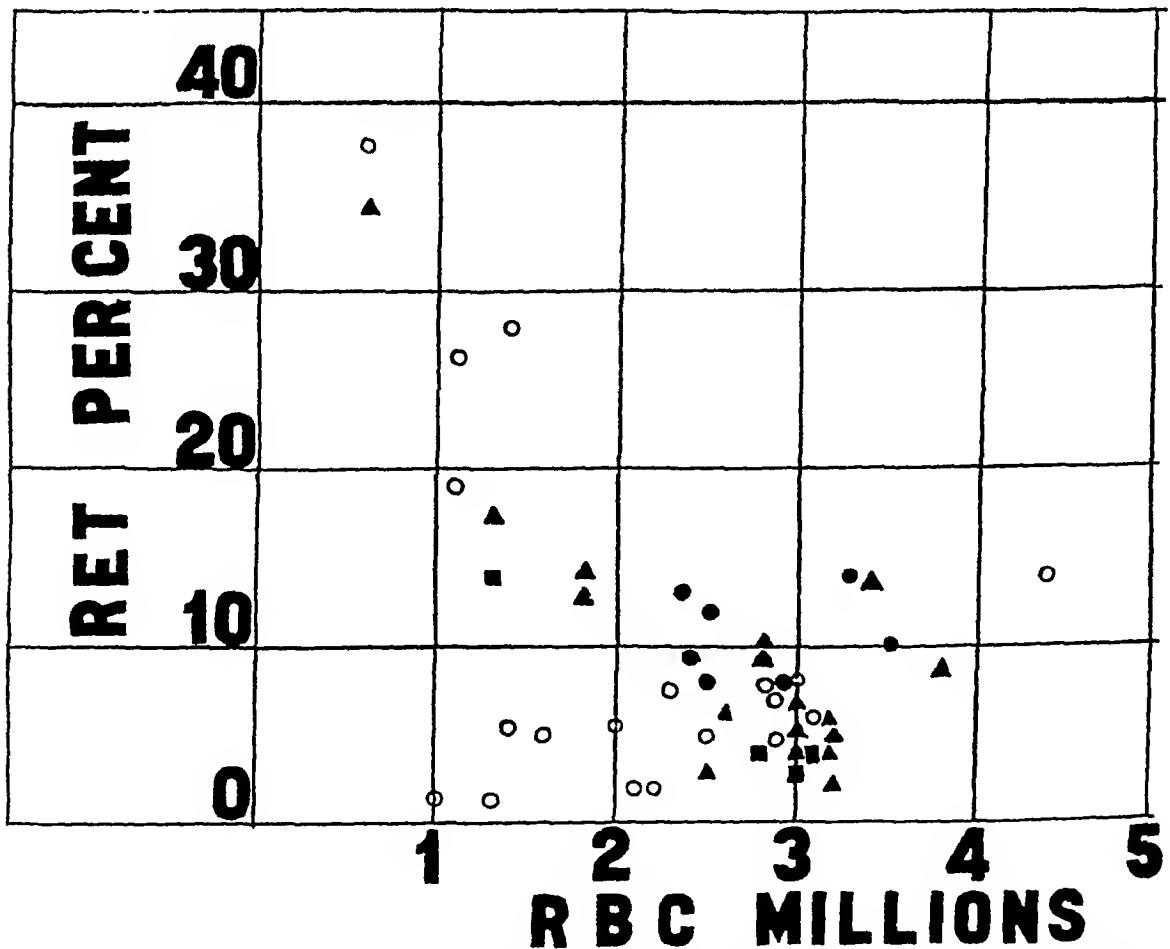


CHART 4 The reticulocyte response in the anemias associated with chronic dysentery, hookworm infestation and tuberculosis of the intestine compared with the response observed in patients with anemia due to malnutrition. The circles represent the response in patients with dysentery, the dots, hookworm infestation, the squares, tuberculosis of the intestine, and the triangles, the anemias due to malnutrition.

the red blood cell count, the higher the reticulocytes rose. There were exceptions among the patients with dysentery when the infection was so severe that death ensued, and when recovery followed blood transfusion. If any conclusions can be drawn from the data it would appear that the cases under discussion responded in the same way as those in which the anemia resulted from malnutrition. I feel, therefore that these observations lend support to the idea that the anemia in the patients with dysentery, hookworm infestation and tuberculous enteritis was of the same nature as that occurring in patients with malnutrition.

Observations of Mettler and Minot¹ are of importance in emphasizing the value of optimum doses of iron in anemia resulting from chronic blood loss and restricted diets, and Strauss² has described its effect in the chlorotic anemias of pregnancy with achylia gastrica, and Powers and Murphy¹¹ have reported positive effects in anemias due to chronic blood loss. My associates and I^{12,13,14} have found that iron was of value in the treatment of anemia due to chronic blood loss, restricted diets, anemia of pregnancy, chronic dysentery, hookworm infestation, chronic chlorosis, and some of the anemias of childhood. Furthermore, in some

TABLE 2
Cases of Anemia Treated With Iron

Diagnosis	Number Treated with Iron	No Showing Improvement	No Showing No Improvement
Dysentery	7	6	1
Hookworm	7	7	0
Tuberculosis of Intestines	4	0	4

In studying the response of the anemia to treatment it was plain that no single form of treatment produced a positive effect in all cases. For example, in the anemias associated with dysentery, positive responses were observed following liver extract potent for pernicious anemia, or iron, or various combinations of whole liver and iron.

The effects of iron therapy in some of the cases are instructive. It has been recognized for many years that iron is of value in the treatment of many forms of anemia, but recently an attempt has been made by various observers to define its usefulness with greater precision. The recent ob-

servations of Mettler and Minot¹ are of importance in emphasizing the value of optimum doses of iron in anemia resulting from chronic blood loss and restricted diets, and Strauss² has described its effect in the chlorotic anemias of pregnancy with achylia gastrica, and Powers and Murphy¹¹ have reported positive effects in anemias due to chronic blood loss. My associates and I^{12,13,14} have found that iron was of value in the treatment of anemia due to chronic blood loss, restricted diets, anemia of pregnancy, chronic dysentery, hookworm infestation, chronic chlorosis, and some of the anemias of childhood. Furthermore, in some

cases, we have found that the effect of iron may be enhanced by the addition of whole liver. The results of iron therapy are recorded in table 2. It was given in the form of ferrous carbonate pills ranging between two and five grams a day. The data clearly show that it was effective in the treatment of anemia associated with hookworm infestation, and in some of the anemias due to chronic dysentery. It was ineffective in the patients with tuberculosis of the intestine but in these patients no form of treatment was beneficial due to the severity of the infection.

The results of iron therapy upon the anemia associated with hookworm in-

festation were uniform and in some patients the effect was enhanced by liver. It is noteworthy that this could be accomplished while the patients continued to carry the worms. That iron is a valuable therapeutic agent in the treatment of anemia due to hookworm infestation is common knowledge and the papers of Day and Ferguson¹⁵, Dock and Bass¹⁶, Kobayashi¹⁷, Keefer and Yang¹², Keefer, Huang, and Yang⁹ furnish ample evidence to confirm this statement.

It is clear, then, that iron is a valuable therapeutic agent in the treat-

ment of some of the anemias associated with gastrointestinal disorders, but if it fails, other substances such as liver or liver extract should be administered.

SUMMARY AND CONCLUSIONS

Malnutrition is often an important factor in the production of anemia associated with disorders of the gastrointestinal tract such as chronic dysentery, hookworm infestation, and tuberculosis of the intestine.

Iron and liver therapy can accelerate hemoglobin regeneration in some of the cases.

BIBLIOGRAPHY

- ¹MINOT, G. R., and MURPHY, W. F. Treatment of pernicious anemia by a special diet, *Jr Am Med Assoc*, 1926, lxxxvii, 470.
- ²CASTLE, W. B. Observations on the etiologic relationship of achylia gastrica to pernicious anemia. I The effect of the administration to patients with pernicious anemia of the contents of the normal human stomach recovered after the ingestion of beef muscle, *Am Jr Med Sci*, 1929, clxxviii, 748.
II The effect of the administration to patients with pernicious anemia of beef muscle after incubation with normal human gastric juice, *Am Jr Med Sci*, 1929, clxxviii, 764.
III The nature of the reaction between normal human gastric juice and beef muscle leading to clinical improvement and increased blood formation similar to the effect of liver feeding, *Am Jr Med Sci*, 1930, clxxx, 305.
- ³STRAUSS, M. B. Chlorotic anemia of pregnancy, *Am Jr Med Sci*, 1930, clxxx, 818.
- ⁴METTIER, S. R., and MINOT, G. R. The effect of iron in blood formation as influenced by changing the acidity of the gastric contents in certain cases of anemia, *Jr Clin Invest*, 1929, vii, 510.
- ⁵METTIER, S. R., and MINOT, G. R. The effect of iron on blood formation as influenced by changing the acidity of the gastroduodenal contents in certain cases of anemia, *Am Jr Med Sci*, 1931, clxxxii, 231.
- ⁶WAUGH, T. R. Hypochromic anemia with achlorhydria, *Arch Int Med*, 1931, xlvii, 71.
- ⁷DARLING, S. T.; BAKER, M. A., and HACKER, H. P. Hookworm and malaria research in Malaya and the Fiji Islands. Report of Uncinariasis Commission to the Rockefeller Foundation, International Health Board, 1920.
- ⁸SCHAPIRO, L. Hookworm infestation in an Indian (Guam) and non-Indian population of Panama, *Am Jr Trop Med*, 1930, x, 365.
- ⁹WELLS, H. S. An observation which suggests an explanation in hookworm disease, *Science*, 1931, lxxiii, 16.
- ¹⁰KEEFER, C. S., HUANG, K. K., and YANG, C. S. The importance of undernutrition in the production of anemia associated with chronic dysentery and tuberculosis of the intestine, *Nat Med Jr China*, 1929, xv, 743.
- ¹¹METTIER, S. R., MINOT, G. R., and TOWNSEND, W. C. Scurvy in adults, espe-

- cially the effect of food rich in vitamin C on blood formation, Jr Am Med Assoc, xcv, 1089
- ¹¹POWERS, J H, and MURPHY, W P Treatment of secondary anemia, Jr Am Med Assoc, 1931, xcvi, 504
- ¹²KEEFER, C S, and YANG, C S The value of liver and iron in the treatment of secondary anemia, Jr Am Med Assoc, xciii, 575
- ¹³YANG, C S, and KEEFER, C S Liver and iron in the treatment of secondary anemia, Nat Med Jr China, 1929, xv, 721
- ¹⁴KEEFER, C S, HUANG, K K, and YANG, C S Liver extract, liver ash, and iron in the treatment of anemia, Jr Clin Invest, 1930, ix, 533
- ¹⁵DAY, H B, and FERGUSON, A R The treatment of ankylostoma anemia, Lancet, 1914, ii, 82
- ¹⁶DOCK, G, and BASS, C C Hookworm disease, 1910, C V Mosby, St Louis
- ¹⁷KOBAYASHI, TOSHIYO Sur les phenomenes regeneratifs des hematies dans les anemies de l'Ankylostomiasse, Le Sang, 1929, ii, 129

On the Morbid Anatomy of the Diaphragm*†

By BALDUIN LUCKÉ, *Philadelphia, Pa*

THE diaphragm is probably the most interesting and important of all skeletal muscles. Its general physiological properties are unique¹, it plays a prominent part in a variety of functions of the body. Thus, it is the chief muscle of respiration, and it acts as an important circulatory muscle by propelling venous blood and lymph into the chest cavity. While the physiology of the diaphragm has received much attention, the pathology of this organ has been greatly neglected, with the exception of reports on diaphragmatic hernia and subphrenic abscess, there are but few studies concerning its morbid anatomy. Yet here, as in other organs, a thorough knowledge of morbid structure is a necessary pre-requisite to an understanding of the functional disorders attendant on disease.

It is true that there are relatively few disease processes which affect the diaphragm as primary lesions, but secondary lesions are extraordinarily common. The majority, though not all, of the diseases of the diaphragm are spread from adjacent tissues and

organs in intimate contact with it: the pleurae, the pericardium, the peritoneum, the liver, gall-bladder, stomach, spleen, adrenals, kidneys, pancreas and duodenum.

In the present communication are discussed some of the more common lesions occurring in the diaphragm, namely secondary neoplasm, tuberculous and acute inflammatory reactions, and certain degenerations. In all of these conditions the diaphragmatic muscle suffers impairment or destruction, and hence its function is interfered with to a greater or lesser degree.

NEOPLASMS

Primary tumors of the diaphragm are very rare. There have been reported less than a score of them, all of the connective tissue series: fibromas, chondromas, lipomas and sarcomas. Secondary tumors, on the other hand, are of far more common occurrence than is generally thought. Thus in a series of 164 pathologic diaphragms, I found eighteen secondary tumors. The growths were carcinomas in fourteen and sarcomas in three instances; the remaining tumor was a renal hypernephroma. Of the fourteen carcinomas, five were primary in the stomach, two each in liver, gall-bladder and ovaries, and one each in the lung, esophagus and small intestines. The sarcomas

*Presented at the Baltimore Meeting of the American College of Physicians, March 25, 1931.

†From the Laboratory of Pathology, School of Medicine, University of Pennsylvania, and the Laboratory of Pathology, Philadelphia General Hospital.

were two primary lymphosarcomas of the mediastinum, and one a spindle cell sarcoma of the thigh. In a series of 12 metastatic cancers of the diaphragm reported by Kitam², five were primary in the stomach, three in the breast and one each in the uterus, gall-bladder, bronchi and tongue. Thus in both Kitam's and the present group of tumors the primary tumor was conspicuously most often located in the stomach.

In some of the cancers arising from the stomach, liver and gall-bladder it was difficult to decide whether the tu-

mors had spread to the diaphragm by direct extension or by metastasis. In the other tumors metastatic distribution was certain.

The gross appearance of the diaphragm varied considerably. In the cancers there was generally a diffuse flat-nodular infiltration beneath one or both serous surfaces (figure 1). Since the majority of these tumors had their primary seat in abdominal organs abutting on the diaphragm the peritoneal surface was generally more heavily infiltrated than the pleural surface. Microscopic examination showed the



FIG 1 Secondary adenocarcinoma of diaphragm. From a white man aged 70 years. The primary tumor was an ulcerating cancer of the pylorus. There were metastases to the liver, both lungs, the retrosternal lymph nodes and the capsule of the spleen. The photograph shows the abdominal surface of the diaphragm invaded by flattened tumors.

masses occupying the subserous lymph-channels. From these they ramified, again largely by way of lymphatics, throughout the diaphragmatic muscle (figure 2) grossly appearing as irregularly distributed whitish bands or nodules. While the lymphatics appear to play the chief rôle in the dissemination of carcinoma through the diaphragm, as suggested many years ago by Rajewsky³, two tumors in the present series were probably distributed by way of the blood-stream, namely, the hypernephroma and the spindle cell sarcoma.

Not all of the neoplasms had the gross appearance described above, two of the sarcomas occurred as isolated large roundish masses each the size of a lemon.

The degree of destruction of the diaphragm was generally considerable. The appearance shown in figure 2 is typical of the majority of the cases. It is seen that large areas of the muscle are completely replaced by tumor cells.

TUBERCULOSIS

Tuberculous involvement of the diaphragm is nearly always secondary to some tuberculous focus in adjacent tissues. In the present series the diaphragm showed tuberculous lesions in 35 cases out of a total of 164 diaphragms examined. Curiously, the peritoneal surface was more often affected than the pleural surface, even when the primary focus was in the lung or the pleura. Thus in the case illustrated by figure 3 the abdominal side of the diaphragm was plastered with caseous flat masses, while the pleural surface was smooth and glossy. The primary focus in this case was a tuberculous bronchopneumonia. The gross appearance of the tuberculous lesions was the same as in tuberculosis of serous surfaces in general; there were found isolated miliary and conglomerate tubercles, or more often a true tuberculous serositis. In the later case one or the other surface of the diaphragm was coated with a thick



FIG 2 Metastatic carcinoma of diaphragm, primary in bile-ducts. From a white man, 53 years old. There were metastases to the lungs, mediastinal, retroperitoneal and mesenteric lymphnodes. The photograph (low power) shows the tumor masses largely confined in greatly distended lymphatics. There is extensive replacement of diaphragmatic muscle.

yellow caseous exudate in which no discrete tubercles were found (figure 4) In either form, adhesions to the lung, the liver, stomach or other adjacent organs were commonly observed

In a considerable number of cases the tuberculous lesions were not confined to the serous surfaces, but tubercles were actually present within the diaphragmatic muscle, not infrequently causing much destruction It is very probable that the frequency of muscular involvement is due to the rich

lymphatic supply through which the infection is distributed Indeed of all muscles, the diaphragm probably is most often the site of tuberculous lesions, for tuberculosis of the skeletal muscles is of rare occurrence'

ACUTE INFLAMMATORY REACTIONS AND THEIR CONSEQUENCES

The occurrence of "diaphragmatic pleurisy" and of "diaphragmatic peritonitis" has long been recognized Inflammation of the muscle of the diaphragm however has received very

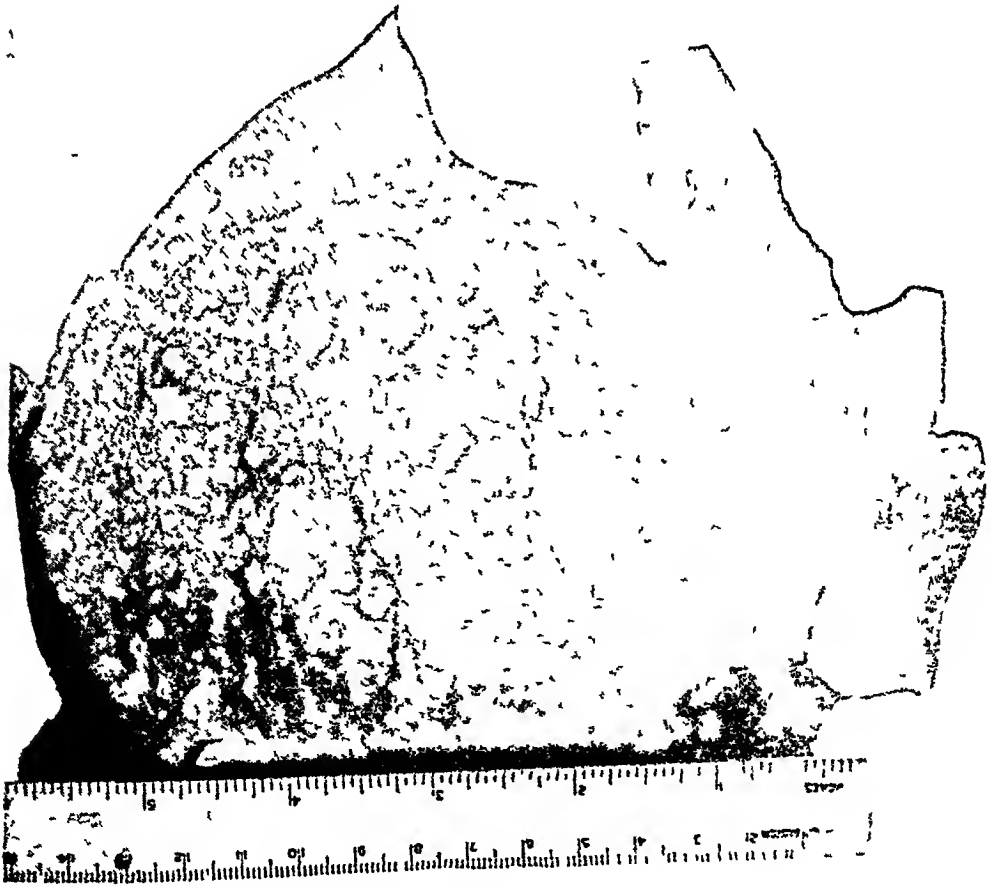


FIG 3 Tuberculosis of diaphragm The peritoneal surface is studded with nodules and conglomerate tubercles between which an exudative reaction may be seen in a negro, aged 26 years, with primary tuberculosis bronchopneumonia Histologic examination showed extensive invasion of the muscle

little attention, although Rohrer⁵, and later Coplin⁶, described in detail the muscular changes generally complicating inflammation of the serous covering. In the present series there were 25 instances of diaphragmitis. Not only was there an inflammation of one

quently a delicate fibrin net could be seen between the muscle fibres. The capillaries were engorged, and the lymph channels prominently distended.

In our series the primary lesion was pneumonia in fifteen cases, peritonitis due to infection of some abdominal

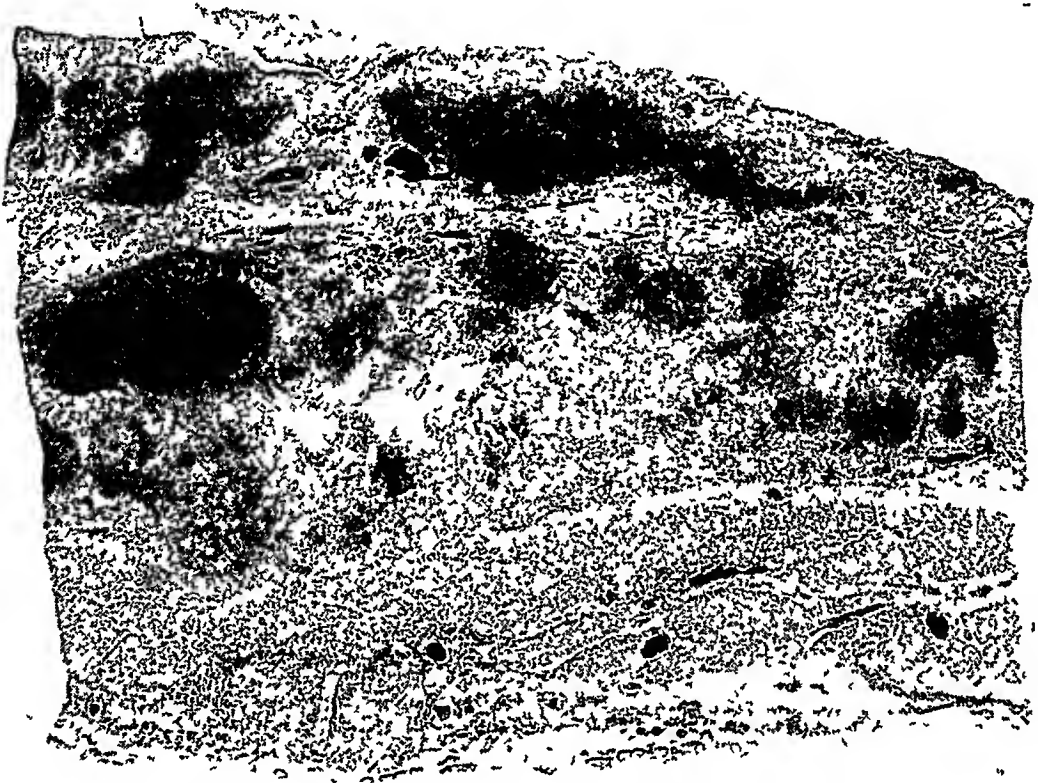


FIG 4 Tuberculosis of both surfaces of diaphragm. From a negro, 26 years old. The pleural surface is covered with a thick layer of caseous material which merges with a caseous tuberculous (visceral) pleurisy. The photograph shows several large caseous areas within the muscle near the pleural surface. The primary lesion was a typical chronic pulmonary tuberculosis, with terminal miliary tuberculosis.

or both serous surfaces, but in every instance the muscle showed definite changes. In some, these consisted chiefly of degenerative lesions, to be discussed in the next section. In the majority there was present in addition a true myositis. The degenerated muscle fibres were separated by an edematous fluid containing polymorphonuclear leucocytes and occasional mononuclear histocytes. Not infre-

quently in eight instances, there was one case of general sepsis due to erysipelas and one case of endocarditis. In the latter two cases the infecting agent was probably conveyed to the diaphragm by the blood-stream.

The inflammatory lesions of the diaphragm are probably of very great clinical importance. Rohrer⁵ believed that such lesions occur in every case of pneumonia, an opinion that I am not

inclined to share. I have found many cases of pneumonia without lesions of inflammatory, as contrasted with purely degenerative, character in the diaphragm. Undoubtedly, however, diaphragmitis is of much greater frequency as a complication of pneumonia than is generally recognized. The degeneration of the muscle cells and their separation by inflammatory edema and exudate probably interfere greatly with the efficiency of muscular contraction.

But not only are the acute lesions of significance, but their consequences are likewise of importance. Organization of exudate covering the serous surfaces leads to adhesions, and the repair of the inflammatory foci in the muscle to patches of fibrosis (figure 5).

DEGENERATIONS AND INFILTRATIONS

It has just been stated that various degenerative changes occur in diaphragmatic inflammation. The most common of them are vacuolar degeneration, cloudy swelling, Zenker's hyaline degeneration and fatty degeneration. Of these vacuolar (hydropic) degeneration was most often seen in the cases of diaphragmitis. Here and there muscle cells were swollen and without structural details, there were smaller or larger irregularly shaped vacuoles within the cells. These vacuoles usually contained a faintly eosin-staining fluid (figure 6). Other muscle cells showed cloudy swelling. This was most readily recognized in fresh unfixed and unstained frozen sections.

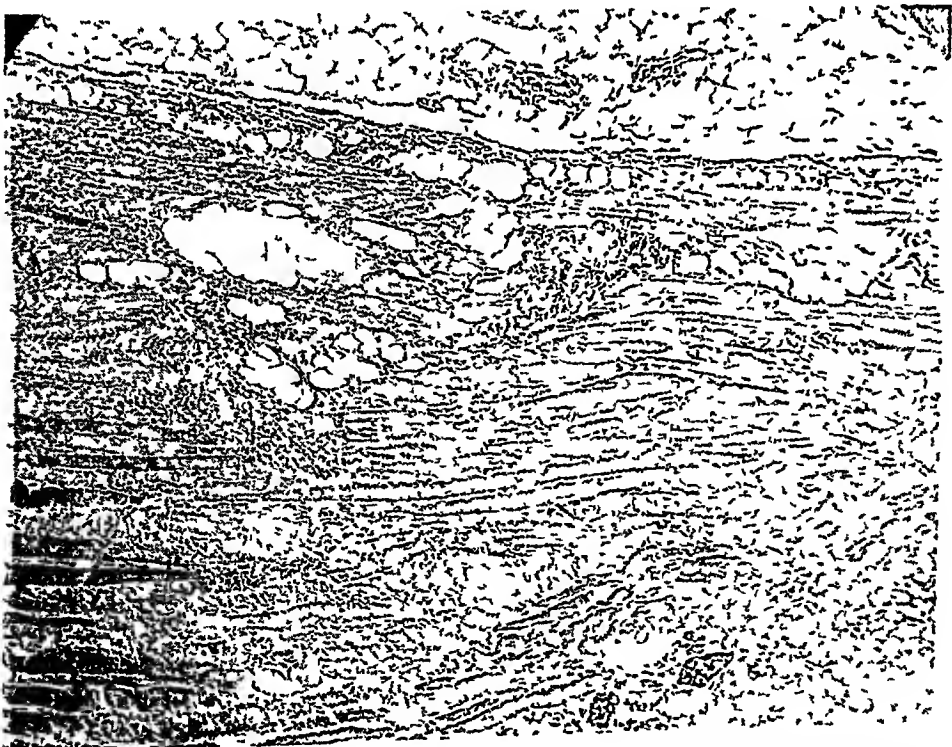


FIG. 5. Subacute diaphragmitis. From a white woman, aged 40 years, who died from widespread lobular pneumonia and staphylococcal abscesses of the lungs. There are scattered small areas of partly organized exudate as well as some older scars. An invasion of fatty-areolar tissue is present.

or teased preparations. The affected cells were large, their striations hazy or entirely lost, the cytoplasm lumpy or granular.

Of the various degenerations of the diaphragm Zenker's hyaline necrosis has received most attention. The subject has been reviewed so recently and so thoroughly by Wells⁷ that no further discussion is here necessary. Wells emphasizes the great frequency with which the diaphragm exhibits this form of degeneration in pneumonia and indicates the probability that such muscular degeneration may be an important factor in determining respiratory failure in this disease.

Besides these acute degenerations, certain changes of more chronic na-

ture are found not infrequently in the diaphragm. These are the so-called fatty degeneration and fatty infiltration. The former is characterized by the appearance of visible fat droplets within the muscle cells, and by many writers is regarded as an indication of irreversible degeneration (Figure 7).

In the present series such fatty degeneration was found most often in cases of severe anemia and in chronic circulatory disturbances, i. e., under the same conditions that fatty degeneration affects the cardiac muscle. Indeed the fatty changes of the diaphragm are very similar to those of the heart; they are patchy in distribution, occurring grossly as yellowish flecks on the cut surface of the reddish-gray diaphrag-



FIG 6 Vacuolar (hydropic) degeneration of diaphragm. From a white man, aged 52 years, who died from extensive lobular pneumonia. The diaphragmatic pleura is covered with a fibrino-cellular exudate. The muscle cells are swollen, vacuolated, and many have a lumpy or hyaline cytoplasm. The intermuscular tissue is edematous.

matic muscle Microscopically, the distribution of the affected fibres is extremely irregular, one usually finds markedly degenerated muscle cells bordered by structurally normal fibres Some fibres contain but traces of visible fat, in others the entire cell is packed with droplets which obscure all details

Fatty degeneration of the diaphragmatic muscle has been studied by a number of observers^{8,9,10,11}, there is general agreement that of all skeletal muscles the most active, the diaphragm, shows this lesion most often

Fatty infiltration is a very different process Under normal conditions the

subserous tissues of the diaphragm contain small amounts of fat, but never in as great a quantity as normally occurs in the subserous areolar tissue of the heart Under certain conditions there may accumulate a considerable layer of fat, which, when the muscle fibres are atrophic, penetrates between them, thus interrupting their continuity

DISCUSSION

It is very difficult to evaluate the significance of the lesions described Certainly it is true that the efficiency of the diaphragm depends above all on the ability of its component muscle fibres to contract properly In tu-

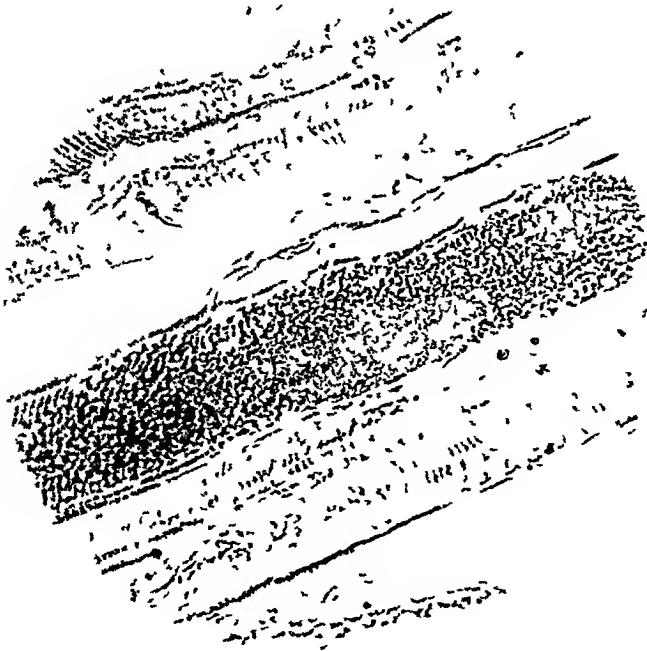


FIG 7 Fatty degeneration of diaphragm (Sudan III stain of frozen section) From a white woman, 62 years old, who had suffered from myocardial disease for several years She died from decompensation and there was marked dilatation of the heart, the myocardium had a striking mottled yellow to yellow-brown appearance, the tigered mottling was best seen beneath the endocardium of the papillary muscles Microscopically there were numerous typically fatty degenerated muscle fibres in the diaphragm usually lying alongside of structurally normal fibres

mors, in tuberculosis, in diaphragmitis and in degenerations it may be assumed that the functional powers of the muscle as a whole are considerably impaired, for all of these disease processes are attended by loss of contractile substance. Such impairment of diaphragmatic function may have serious consequences when the respiratory or circulatory mechanism is at fault.⁶ Unfortunately it is very difficult to determine after the death of the patient from clinical records what ef-

fect any diaphragmatic lesion discovered post mortem had on the course of the disease. The true significance of diaphragmatic lesions is yet to be worked out, and this can be done only through experiment and through collaboration of clinician and pathologist in a large series of cases.

*For a discussion of the pathological physiology of the diaphragm reference should be made to the monographs of Eppinger¹² and of Hitzenberger¹³, as well as to the writings of Landis¹⁴.

REFERENCES

- ¹LEE, F S, GULNTHNER, A E, and MELEN-
EY, H E. Some of the general physio-
logical properties of diaphragm muscle
as compared with other certain mam-
malian muscles, *Am Jr Physiol*, 1916,
xl, 446-473
- ²KITAIN, H. Zur Kenntniss der Häufigkeit
und der Lokalisation von Krebsmetasta-
sen mit besonderer Berücksichtigung
ihres histologischen Baus, *Virchow's
Arch*, 1922, ccxxxviii, 289-309
- ³RAJEWSKY, A. Über sekundäre Krebsent-
wicklung im Diaphragma, *Virchow's
Arch*, 1876, lxvi, 154-171
- ⁴MEYENBURG, H. VON. Die quergestreifte
Muskulatur, Henke, F and Lubarsch, O,
Handb d spez Pathol, Anat u Hist,
vol 9, pt 1, 1929, J Springer, Berlin
- ⁵ROHRER, C W G. Inflammation of the
diaphragm complicating pneumonia,
Maryland Med Jr, 1901-2, xlv, 391-397
- ⁶COPLIN, W M L. Changes in the inter-
costal muscles and diaphragm in in-
fective processes involving the lung and
pleura, *Proc Path Soc Philadelphia*,
1904, vii (N S), 65-81
- ⁷WELLS, H G. Waxy degeneration of the
diaphragm a factor in causing death in
pneumonia and in other conditions
Arch Path, 1927, iv, 681-686
- ⁸CALLANDER, G W. On fatty degeneration
of the diaphragm, *Lancet*, 1867, i, 39-40
- ⁹ZAHN, WILH. Die degenerativen Ver-
änderungen der Zwerchfellmuskulatur,
ihre Ursachen und Folgen, *Virchow's
Arch*, 1878, lxxiii, 166-180
- ¹⁰FALKENSTEIN, S. Ein Beitrag zur Path-
ologie des Zwerchfelles, I-D, Bonn,
1904
- ¹¹KOLODNY. Über die Verfettung der will-
kürlichen Muskulatur, *Virchow's Arch*,
1922, ccxxxvi, 270-278
- ¹²EPPINGER, HANS. Allg u Spez Pathol d
Zwerchfelles, *Supl to H Nothnagel
Spez Path u Therap*, 1911, Alfred
Hoeber, Wien u Leipzig
- ¹³HITZENBERGER, KARL. Das Zwerchfell, im
gesunden und kranken Zustand, 1927,
J Springer Wien
- ¹⁴LANDIS, H R M. Disease of the dia-
phragm, Osler, Wm, *Modern Medicine*,
3rd ed, 1927, vol iv, 334-345, Lea and
Febiger, Philadelphia
- NORRIS, G WM, and LANDIS, H R M.
Diseases of the chest, Chapt xxiv, pp
682-705, 3rd ed, 1924, W B Saunders
Co, Philadelphia

The Heart and the Diaphragm*†

By I M TRACE, M D , F A C P , *Chicago, Ill*

WALSH, writing in 1871 about the clinical importance of the diaphragm, said "I am persuaded much of their silence depends less on immunity from disease of this musculo-fibrous septum, than upon the rarity with which it is examined post-mortem. Clinical ignorance is the necessary result of this neglect." And even at present the diaphragm hardly gets the clinical considerations its location and functions warrant.

A musculo-fibrous structure, lined with pleuro-pericardial serosa on its upper and peritoneum on its lower surface, it separates the thoracic and abdominal cavities and is in close contact with the cardio-respiratory organs and important abdominal viscera.

Symptomatically sharing the troubles of its neighbors on the north or the comrades on the south, it may be visited by such remote calamities asiliary tuberculosis, trichiniasis, pernicious anemia and scurvy. It is said to undergo degeneration in severe congestive heart failure and marked emphysema (Zahn, Falkenstein, Hitzemberger¹).

The phrenic is its chief motor nerve and its muscle tone is nicely balanced

by an interplay of the sympathetic and parasympathetic forces.

Next to the heart it is the most important muscle in the body (Falkenstein). Structurally and functionally it bears a rough analogy to the heart muscle. It is striated, its contractions are rhythmic, tetanic in character, of long duration, with short intervals of rest. It works unremittingly from the cradle to the grave, but its action is both voluntary and involuntary. Considered at one time the main muscle of respiration, its importance was somewhat dimmed by the surgeon. Unilateral paralysis was found to be no great handicap and even bilateral phrenicotomies were survived. The diaphragm is one of the important muscles of respiration and its chief business is to keep the lower lobes inflated and properly aerated.

The circulatory function of the diaphragm is often lost sight of. The upright posture of man makes the backflow of venous blood difficult. During an inspiratory diaphragmatic contraction the intra-abdominal pressure increases, the intrathoracic becomes negative and the diaphragm acts as a suction pump upon the returning venous blood. The liver, the great reservoir of venous blood, is compressed by the diaphragm, "like a wet mushroom by a grasping hand."

*Read before the Chicago Medical Society, March 18th, 1931.

†Received for publication, April 20, 1931.

(Wenckebach), and its blood is forced out into the great veins of the thorax. With each diaphragmatic contraction the intra-abdominal cavity is enlarged and the intracardiac pressure is diminished, with the heart moving caudally, thus facilitating the better filling of the heart chambers.

The pressure within the abdomen varies with inspiration, body positions and distention of the hollow viscera. The intrapulmonary pressure is subject to marked and at times sudden variations. There is a reciprocal and antagonistic relationship between the heart and the diaphragm, and thus between the two cavities, by the diaphragmatic abdominal reflex of Sherrington. A positive hypertonic reflex of the diaphragm is often associated defensively with a negative hypotonic cardiac reflex (dilatation) and a positive hypertonic cardiac reflex is helped by a negative hypotonic diaphragmatic reflex. The diaphragm thus acts as a buffer, protecting the thoracic viscera from excessive intra-abdominal pressure and the abdominal contents from sudden variations in intrapulmonary pressure.

To function efficiently the diaphragm must be unhampered in its movements and maintain an optimum position in the thorax. Its central tendon is at the eighth dorsal spine and it reaches the fourth interspace on the right, the fifth rib on the left anteriorly; posteriorly, the eighth rib on the right and the eighth interspace on the left. Its position is the result of the normal pulmonary pull, muscle tone, and the width of the lower thorax. It varies with the pressure in the thoracic and abdominal cavities and is marked-

ly influenced by posture⁴, being lowest when the person is standing and highest when he is supine; sitting produces no appreciable change in the normal diaphragm.

Even from this fragmentary anatomico-physiologic survey it is quite evident that the diaphragm is a friendly intermediary and helpful ally, and it is hardly surprising to find it parading at times in the clinical garb of its neighbors, especially the heart.

Young adults and children not infrequently have pain in the lower axillary regions on walking or running. When the pain is on the left side the heart comes under suspicion. If the heart is found normal, as it usually is, the pain is due to spasm of the diaphragm.

A fit of laughter is likely to provoke similar discomfort as the following case will illustrate.

A Gypsy of forty-five, complained of pain in the precordium, radiating to the shoulder, of three days' duration. The pain was severe and was aggravated by exertion, by loud and fast talking. The cardio-circulatory apparatus was normal. Further questioning brought out that while in a speak-easy, swapping stories with his comrades, an especially good one caused a fit of laughter and the pain appeared shortly after. The fluoroscope showed jerky movements of the left diaphragm. Strapping relieved the pain immediately.

In effusive pericarditis the diaphragm may become inflamed by contiguity. Nausea, vomiting and hiccoughing may dominate the picture and obscure the diagnosis. When with the diaphragmitis there is also a phrenic involvement, pain in the shoulder and dysphagia may be so severe that the mere sight of water or

food will cause pain, the so-called hydrophobic type of an effusive pericarditis⁶ Swelling and tenderness of the liver may come on before fluid can be demonstrated in the pericardial sac clinically and be quite puzzling It is due to an embarrassment of the vena cava inferior by the faulty movements of the right diaphragm

The sequence of events may be reversed A left sided diaphragmatic lesion may cause severe heart pain

A man of twenty-four was awakened at two in the morning with severe anginal pain radiating to the shoulder, which required morphia The pain recurred two or three times daily for about three weeks, the patient running a septic temperature The chest showed nothing abnormal Fluoroscopy was likewise negative, the left diaphragmatic outline being clear, regular in outline and its lateral half moving freely with some haziness in the left costo-phrenic angle The needle obtained 5 cc of slightly cloudy fluid Three weeks after the onset, edema appeared in the epigastrium, slight bulging soon following Incision revealed pus in the left subdiaphragmatic space close to its central portion With drainage the fever subsided, the pain disappeared and the recovery was speedy The cause of the abscess remained obscure

When a chronic pericarditis works through the diaphragm and involves the capsule of the liver, Pick's pseudocirrhosis is likely to result Its classical diaphragmatic phenomena of epigastric systolic retraction during inspiration and Broadbent's systolic tug posteriorly are familiar to every clinician It is not generally known that occasionally an unaccountable right pleural effusion⁷ may be its earliest manifestation, more so when associated with an enlarged liver The compromised right diaphragm apparently interferes with the action of the

right heart or compresses the supra-diaphragmatic portion of the vena cava inferior (Hanot⁸)

Milder forms of an adherent pericardium often entirely escape clinical detection Demonstrating the immobility of the apex by percussion, while often diagnostically helpful, is not always possible in women, in the obese and in the emphysematous The fluoroscope with the patient in the left lateral position will diagnose⁷ the condition with certainty and ease Normally the heart moves away from the dependent left chest on deep inspiration, this movement is most marked in the lower left cardiac contour With an adherent pericardium this movement is slight or entirely absent With the patient in the erect position there may be present an upward systolic tug⁹ of the left diaphragm

Dyspnea may at times be the outstanding symptom of a chronic diaphragmitis It is a good clinical rule to suspect the diaphragm, when the dyspnea is out of all proportion to the findings in the chest

Not infrequently following an effusive pleurisy of some duration, dyspnea appears upon exertion Re-examination shows marked dullness with diminished breath sounds, ectasia is absent, even retraction of the intercostal spaces may be present Fluid is still suspected, but the tap is dry The fluoroscope shows no fluid, but haziness and immobility of the diaphragm Needling, as suggested by the Japanese, stimulates the lazy diaphragm to increase its respiratory excursions and to keep the lungs inflated Pryor describes severe dyspnea in pneumoconiosis involving the diaphragm The

patient is pale, the heart is small and tube-like; the apex beat is feeble and the heart tone distant. When fibroid phthisis invades the diaphragm, dyspnea may become quite troublesome.

Sudden and severe dyspnea is likely to come on following operations on the upper abdomen or injury to the chest wall. The clinician suspects an acute pulmonary atelectasis; the physical findings may, and the x-ray does diagnose the condition. While it is conceded that bronchial obstruction by viscid secretion is the main factor⁹ in the pathogenesis of a massive pulmonary collapse, the defensive splinting of the thoracic wall and of the diaphragm, already handicapped by the supine posture, play no small contributory part by abolishing or diminishing the diaphragmatic excursion and interfering with the efficient respiratory dilatation of the lungs and their ability to expel the bronchial secretion¹⁰. Yandell Henderson¹¹ suggested that carbon dioxide be given at the end of the anesthesia to induce deep respirations and properly inflate the lungs.

Eventration or relaxation of the diaphragm, whether congenital or acquired, is usually left sided. The raised left diaphragm does not compress the pulmonary base but lifts and moves the heart to the right. Most often symptomless, it will occasionally give rise to a cardio-diaphragmatic syndrome of precordial distress, dyspnea and angina-like pain upon a full stomach or intestinal distention in the gonadal and adipose dystrophies and in the myocardiopathies³.

The findings of basal tympany with diminished breath sounds, the apex in the fourth interspace, with the trachea

displaced to the right, while suggestive, are nearly always overlooked and the diagnosis is made by the fluoroscope. The left diaphragm is high, its outline is regular but faint, it may show paradoxical movements and easily moves upward when pressure is exerted upon the abdomen.

Any one past forty with a girth of generous proportions is well acquainted with the discomfort in the chest, fullness of the head and the turgescient face when, on a full stomach, he is called upon to lace a shoe. The increased abdominal pressure moves the diaphragm up and temporarily embarrasses the circulation. Flatulence frequently provokes extrasystoles, and that angina pectoris is more prone to appear upon a full stomach is a well known clinical fact. One wonders if the frequency of acute coronary thrombosis, masked as an acute indigestion, at the height of a generous banquet, is not due to embarrassed filling of already sclerosed coronaries by a distended stomach pressing up the diaphragm against a diseased heart.

Indeed, any factor favoring an increased intra-abdominal pressure is likely to call forth circulatory difficulties, especially in the obese, in those of sthenic habitus, and in the gravidae. Dietlen⁴ maintains that in the obese with dyspnea the poor or absent mobility of the diaphragm brings about deficient pulmonary ventilation and venous disturbances in the thoracic and abdominal cavities.

It is not uncommon to see men of sthenic habitus in the fourth or fifth decade, short of neck, broad of chest, red of face, with tense muscular abdominal walls, complain of some short-

ness of breath and precordial distress upon exertion. The thickened arteries, the aortic configuration of the heart with the apex displaced to the left, and short systolic murmurs heard best or appearing only during expiration, logically enough point to the heart, but the fluoroscope shows a high diaphragm and a squatty left heart silhouette well buried in the diaphragmatic shadow. The electrocardiogram shows left axis deviation. In the obese the third lead may show complete inversion¹².

It is hard to ascertain in these cases just what part the heart plays in the production of the symptoms. It is difficult to absolve it from all guilt, since Pearce³ has shown experimentally that the abdomino-visceral reflex responsible for the clinical syndrome of dyspnea and cardiac distress does not affect the normal heart, but only when the myocardium is injured.

About the seventh month of pregnancy the enlarging uterus widens the lower thorax¹³, flattens and pushes up the diaphragm. The apex is raised and rotated to the left, basal râles and even murmurs may appear (Dietlen¹).

A para two of twenty-six, eight months pregnant, complained of dyspnea upon exertion and edema of the ankles. There was no history of rheumatic infections or previous cardiac discomfort. The heart was apparently out to the left with a short systolic mitral murmur not transmitted. Left axis deviation was present in the electrocardiogram. It was interpreted as a normal heart temporarily mechanically embarrassed by the increased intra-abdominal pressure. Six weeks after delivery the heart and the electrocardiogram were normal and the patient in the best of health.

Another gravida of thirty with a very large abdomen had dyspnea and annoying extrasystoles. Delivery relieved her of both.

Mackenzie¹³ explains the cardiac discomfort in the gravidae by the embarrassment of the right heart by the lessened respiratory movements. The latter obviously are hampered by the high and flattened diaphragm. Normal hearts withstand this temporary load quite well. In diseased hearts with the right ventricle already considerably overtaxed as in mitral stenosis, the increased load may lead to serious cardiac failure or acute suffocative pulmonary edema.

The following case is very instructive.

A para three, with a mitral stenosis, when eight months pregnant developed some cough and dyspnea upon exertion. When almost at term, during an obstetric examination and while flat on her back, she became cyanotic, coughed incessantly, and an alarming pulmonary edema quickly supervened. Only heroic treatment saved the patient. Rest in bed with digitalis carried her to term, when she was delivered by Dr. Louis Rudolph quite uneventfully in a semi-sitting position.

The abnormally high diaphragm is not the only source of diaphragmatic dysfunction¹. The low diaphragm when pronounced, is productive of a goodly share of chronic invalidism. Its owner is nearly always thin and pale, with a long and narrow chest and a protuberant potic abdomen. The extremities are cold and the blood and pulse pressure are low. The abdominal organs are palpable. Nearly always the victims of numerous poorly defined digestive complaints, they are not infrequently subjected to many unnecessary and repeated abdominal operations. Frequently circulatory disturbances assert themselves, dizziness, dyspnea, palpitation, and fatigue upon exertion bring them to the physician. These

patients present all the symptoms of an effort syndrome the heart is small, the pulse weak and the muscles flabby. The fluoroscopic examination shows a narrow heart hanging suspended like a drop from the large blood vessels. The diaphragm is low, with poor respiratory mobility, and is definitely separated from the cardiac shadow. The poor filling of the cardiac chambers causes a relative arterial anemia with the subjective sense of exhaustion and the suspended heart, lacking its diaphragmatic support, is likely to produce such bizarre findings as a paradoxical pulse or even a tracheal tug. (Wenckebach¹) A well applied abdominal support quickly brings relief. Prolonged rest in bed,

hyperalimentation, aided by insulin, as suggested by Falta, often improve the general condition remarkably.

The physician, who in physical diagnosis of the lungs takes into consideration the depth and shape of the thorax, the thickness of the parietes, the position of the heart and the mobility of the diaphragm, may profitably be on the alert in evaluating cardiac symptoms also, in connection with two important factors the position and the mobility of the diaphragm. He will be rewarded by a better understanding of the mechanism of some symptoms and by fewer diagnostic errors, and the patient will profit by more intelligently applied therapeutic procedures.

REFERENCES

- ¹HITZENBERGER, K. Das Zwerchfell in gesunden und kranken Zustand, 1927, J Springer, Wien
- ²LEE, F. S., GUNTHER, A. E., and McLENEY, H. E. Some of the general physiological properties of diaphragm muscle as compared with certain other mammalian muscles, *Am Jr Physiol*, 1916, xl, 446-473
- ³RASUMOV, N. P., and NICOLSKAJA, A. B. Buffer function of diaphragm and cardio-abdomino-diaphragmatic syndrome, *Am Heart Jr*, 1929, iv, 600-611
- ⁴WIGGERS, C. J. Modern aspects of the circulation in health and disease, 1923, Lea and Febiger, Philadelphia
- ⁵CHRISTIAN, H. A. The diagnosis and treatment of diseases of the heart, Oxford Monographs on Diagnosis and Treatment, Vol. iii, 1928, Oxford University Press, New York
- ⁶VAGUEZ, H., and BORDET, E. The heart and the aorta, studies in clinical radiology, Tr. from 2d French ed. by J. A. Honey and J. Muay, 1920, Yale University Press, New Haven
- ⁷BUTLER, P. F., and DANA, H. W. Diaphragm excursions normal and pathologic, *Am Jr Med Sci*, 1928, clxxvi, 569-577
- ⁸SMITH, E. S. Cardiolytic for chronic mediastinopericarditis, with report of two cases and review in literature to date, *Med Clin North America*, 1920, iv, 835-863
- ⁹JACKSON, C., and LEE, W. E. Acute massive collapse of the lungs, a discussion of its mechanism and of its relation to foreign bodies and post-operative complications, *Trans Am Surg Assoc*, 1925, xliii, 723-766
- ¹⁰FUNK, E. H. The diagnosis and treatment of chronic diseases of the respiratory tract, Oxford Monographs on Diagnosis and Treatment, Vol. v, 1929, Oxford University Press, New York
- ¹¹HENDERSON, Y. The physiology of atelectasis, *Jr Am Med Assoc*, 1929, xciii, 96-98
- ¹²BLAND, E. F. and WHITE, P. D. Clinical significance of complete inversion of lead III of human electrocardiogram, *Am Heart Jr*, 1931, vi, 333-337
- ¹³MACKENZIE, J. Heart disease and pregnancy, 1921, H. Frowde, Hodder and Stoughton, London

Malignancy in the Lung: Including Eight Primary Carcinomas With Autopsy Findings*†

By HENRY MONROE MOSERS, A M , M D , F A C P , *Brooklyn, N Y*

ROBERT J Graves, of Dublin, who so clearly described exophthalmic goiter that the condition is still called Graves' Disease, in a clinical lecture¹ on the Practice of Medicine, delivered nearly ninety years ago, wrote "I shall conclude this lecture with the description of a singular and uncommon disease of the lungs. Rare diseases should not be looked upon as mere matters of curiosity, but should be attentively studied with the view of enabling us to recognize the true nature of similar cases when they again occur." He continues, "The diagnosis of encephaloid tumors of the lungs was, a few years ago, completely impossible, but, I trust, that ere long we may be enabled to arrive at some degree of certainty, even in this difficult and obscure branch of thoracic pathology."

Morgagni², (1682-1772) who laid the foundation of pathological anatomy, was probably the first to publish the results of several autopsies on lungs that might be diagnosed as cancerous, and were so interpreted by him

*From the Medical Service, Kings County Hospital, Brooklyn, N Y

†Read at a Meeting of the Brooklyn Society of Internal Medicine, November 28, 1930

It is probable that the first of the cases which he published as cancer of the lungs was really an example of primary lung tumor. In this case, he describes the disease of a man sixty years old, which was accompanied by cough and copious expectoration of a yellowish, rather crude material, rarely but then distinctly stained by streaks of blood. At autopsy, the lung was found extremely hard with adhesions to the pleura and mediastina, and nothing else but an "ulcus cancerosum in the right lung"

Adler³, in his masterful study of Primary Malignant Growths in the Lungs and Bronchi, states that "lung tumors were absolutely unknown in ancient and medieval medicine until the time of Morgagni." This statement is no doubt true from all our known medical literature concerning medical conditions of ancient and medieval times. It seems impossible to the writer that metastatic growths from malignancies in other organs never occurred or were never found in the lungs of those afflicted. It is hoped that at some later date accounts of such new growths in the lungs will be found in the writings of physicians of the ancient times. The belief that

primary neoplasms of the lungs are among the rarest forms of disease has persisted for centuries, and it is only within the last few years that this belief is becoming changed, because of the comparatively great number of tumors of the lung being found and studied. For several years there has been a growing belief that intra-thoracic cancers are increasing in frequency. This belief is being confirmed more and more by recent reliable statistics. In a study of the incidence of primary carcinoma in the lung, Rosahn¹ concludes that "the post-mortem incidence of primary carcinoma in the lung is steadily increasing, and this increase is real and absolute." Whatever may be the explanation, primary carcinoma in the lung is more common now than formerly. The cause of this greater frequency of occurrence is not known. This increase was commented upon by Adler² who published his study in 1912, and who did not suggest any reason for it. Davidson³, of London, in a study of

cancer in the lung, published in 1930, states that "it seems reasonable to suppose that for an explanation of the increase of primary carcinoma in the respiratory tract, we must look to some factor which, since the period of the War has begun to operate in greater degree, and which, through the production of specific tissue irritation, may account for this hitherto unusual localization of malignant disease in such individuals as are especially susceptible."

In a large, general hospital such as the Kings County Hospital, with an average daily census of 1710 patients, ample opportunities are presented for the study of malignant conditions in the lungs, whether primary or secondary. It has been the privilege of the writer to review the appearance of malignant diseases at the Kings County Hospital during the decade from 1920 to 1930, and in addition to include eleven months of 1930. The following figures are presented of malignant tumors, Kings County Hospital

TABLE I
Evidence of Malignant Tumors and of Metastases

Year	Patients	Tumors	Metastases To		Metastases General
			Other	Organs	
1920	10698	232		37	—
1921	13931	279		13	—
1922	16200	298		19	—
1923	18131	312		42	—
1924	19594	396		68	13
1925	19969	437		85	6
1926	19715	373		75	4
1927	21236	406		96	10
1928	23719	355		48	11
1929	24948	334		66	15
	188241	3422		549	59
1930 to Nov 1st	24288	245			

TABLE II
Metastases to the Respiratory System

Year	Lung	Pleura	Larynx	Trachea
1920	—	—	—	—
1921	4	—	—	—
1922	6	—	—	—
1923	2	1	—	—
1924	5	—	1	—
1925	3	1	—	1
1926	3	—	1	—
1927	5	—	1	—
1928	6	1	1	—
1929	5	2	1	—
	—	—	—	—
	39	5	5	1
1930 to Nov 1st	10	—	—	—

TABLE III
Malignant Tumors of the Respiratory System

Year	Lung	Larynx	Pleura	Epiglottis
1920	2	3	—	—
1921	1	3	—	—
1922	6	10	—	—
1923	—	5	1	—
1924	9	7	—	1
1925	7	5	—	—
1926	6	5	—	—
1927	3	4	—	—
1928	7	4	—	1
1929	6	12	2	—
	—	—	—	—
	47	58	3	3
1930 to Nov 1st	7	12	—	1

Patients with malignant tumors in the lungs may be divided into three general classes for diagnosis

First, those upon whom a diagnosis can be made only on post-mortem examination, because of the absence of any general or pulmonary symptoms, except weakness and emaciation, or because the patient is seen only when moribund, and the usual physical findings of malignant tumor in the lungs are masked by other conditions

Second, those upon whom a diagnosis can be made easily by reason of evidence of tumor growth in other parts of the body, in addition to the pulmonary findings

Third, those upon whom a diagnosis of new growth in the lungs can be made because of the history, the course of the disease, the physical findings and the absence of tumor growth in other organs

The presence of a malignant tumor in the lung is not always an easy matter of diagnosis, and unless the growth causes enough discomfort for the patient to seek a physician, the condition may not be discovered during life

CASE REPORTS

Case I On November 22, 1927, M. J., a woman 82 years old was admitted to the County Hospital with a cellulitis of the scalp. Ten days before admission

tient had fallen down stairs and had received a scalp wound which became infected. The cellulitis was properly cared for, but the patient's general condition was poor, apparently due to her eighty-two years of age. Three days before her death, or seventeen days after her admission to the hospital, the patient was drowsy, became comatose and died. The belief was that she had a generalized atherosclerosis and died from kidney failure. However, we were fortunate enough to have permission for a post-mortem examination. The histological findings of interest to us at the present time are as follows. The lungs showed emphysema, chronic fibroid pneumonia, congestion and edema and an area of epidermoid carcinoma. The liver showed chronic passive congestion. The kidneys showed a chronic glomerulonephritis. Here we have a primary carcinoma of the lung, in a patient who apparently had no pulmonary symptoms.

Case II Another patient, No 59663-30, autopsy No 8734-30, a man, age 52 years, was admitted to Kings County Hospital and died forty-eight hours later. He was extremely pale, was struggling for air, and had been drinking large quantities of whiskey for more than a month. He was a chronic alcoholic. His condition was critical on admission. His blood pressure was 80/60. He became unconscious shortly after entering the hospital but could be aroused. His red blood cells were 1,060,000 and his hemoglobin was 35 per cent. A history obtained from his family reported a gastric hemorrhage and bloody stools about one month before admission. He complained of pain in the abdomen. The patient did not show emaciation. During his short stay in the hospital, he was restless and fighting for air. There were many coarse, moist râles throughout both lungs. The object of treatment of this patient was to support and stimulate him over the emergency. However, he died forty-eight hours after admission. Our feeling was that he had a severe anemia, a chronic alcoholism, with an alcoholic wet brain. A post-mortem examination was permitted, of which the points of interest to us now are "The right lung shows infarcted areas at the base, which are well circumscribed, and adjacent to this is

found a cavity from which pus escapes. At about the centre of the middle lobe, there is a tumor-like mass, five and one-half centimeters in diameter. This mass is firm, nodular and white in color. The pleural surface of the left lung is thickened and rough. On section, a frothy fluid can be expressed from the cut surfaces. The ribs and vertebrae have tumor-like growths. The diaphragm, also, shows raised nodular masses which are hard. There is no gross pathology of the trachea or esophagus. The mucosa of the stomach near the pyloric end and the duodenum show denuded areas suggestive of old ulcer formation, the remainder of the gastro-intestinal tract is grossly normal. Histologically, the patient showed acute purulent bronchitis, pulmonary abscess, confluent broncho-pneumonia, metastatic lymphosarcoma in the lung, lymphosarcoma of the peribronchial glands, metastatic lymphosarcoma of the bones and chronic ulcer of the duodenum. Here we have another patient upon whom the diagnosis of malignant tumor in the lung could not be made because of his condition on admission to the hospital. Ewing,⁶ in his book on Neoplastic Diseases, states that "frequently these new growths are discovered only at autopsy." Adler³ states "one form that occurs occasionally is that of a single nodule, usually quite small surrounded perhaps by a few minute malignant nodules deeply buried in the lung tissue of one lobe, producing only very slight or possibly no symptoms during life, and as a rule, discovered by mere accident at autopsy."

There are some patients upon whom the diagnosis of malignant tumor in the lung is not difficult to make.

Case III A young man, No 56734-30, a laborer, 21 years old, was admitted to Kings County Hospital, August 13, 1930, with the following complaints: Weakness, pain in the chest and in the abdomen, and loss of thirty pounds weight in six months. On January 10, 1930, the patient was operated upon for hernia complicated by an undescended testicle, and a varicocele operation was performed. On July 27, 1930, at Kings County Hospital, his left testicle was removed. Following this operation, he had pain almost contin-

uously in the abdomen and in the flanks. One week before admission, on August 13th, pain appeared in the lower part of the chest on both sides. Upon auscultation, the patient had numerous râles throughout the left lower lobe, and râles below the scapula on the right side. There was a lump at the upper angle of the scar of the operation on the testicle.

A résumé of the radiographic reports follows. Numerous well defined nodular metastases are strewn throughout both lungs, these nodules varying from approximately 1 to 4 cm in diameter, being definitely spherical, borders well defined, these are more commonly situated near the periphery. Osseous system examination fails to reveal any evidence of abnormality of texture of the bones of the skull, extremities or trunk. Conclusions. Nodular type of pulmonary metastases, probably the result of sarcomatous infiltration. (See figure 1.)

This man died October 26, 1930, seventy-four days after admission to the hospital and ninety-one days after removal of the testicle. The diagnosis with this patient was not difficult, as the pathological report from the section of removed testicle is as follows: "The section shows testicle and epididymis. The testicular portion shows no marked change from the normal. The epididymis, however, presents a neoplasm composed of varying types of cells, some being large and round, some showing eccentric nuclei and rather horse-shoe shaped, and still others showing cells not unlike those known as the reticulum cells of lymph nodes. Hyperchromatism is quite a marked feature. There are numerous areas of necrosis. The neoplasm is definitely histoid in morphology. The diagnosis of the tumor is polymorphocellular sarcoma." With this young man, it was not difficult to make a diagnosis of metastatic sarcoma in the lungs.

Case IV Another type of patient, No 24877-29, Autopsy No 7796-29, admitted to the Kings County Hospital, was a woman forty-seven years old, who complained of pain in the chest, weakness, loss of weight and dyspnea. This patient died seven days after admission to the hospital. She had had a breast amputated six months previously for carcinoma. The autopsy revealed metastases

to the lungs, heart, liver, adrenals and mesentery. A diagnosis, before death, of metastatic carcinoma in the lung was not difficult.

Although we know many times that we have a metastatic tumor in the lungs from a primary malignant growth elsewhere in the body, the classification of the type of tumor is not always as easy a matter as in the two preceding patients.

Case V A man, No 5989-28, Autopsy No 7291-28, forty-six years old, was admitted to Kings County Hospital complaining of pain localized in the right chest and upper abdomen about the costal margin, and included between the anterior and posterior axillary lines. This pain had persisted for two weeks and was described as if needles were sticking into him. The patient stated that at the onset of this attack he had vomited for five days. There was no blood in the vomited material. On admission, the patient did not appear acutely ill but did show signs of emaciation. A slight cough was present. He had signs of fluid in the right pleural cavity. There was marked epigastric and upper rectus rigidity. Later a bloody fluid was removed from the right pleural cavity. The conditions considered as possible were chronic pulmonary tuberculosis, pleural effusion, malignancy in the lung, chronic gall-bladder disease, peptic ulcer and malignancy in the epigastric area. This patient died thirty-one days after admission to the hospital.

A résumé of the radiographic reports follows. Examination of the gastro-intestinal tract fails to reveal any evidence of organic lesion of the stomach, duodenum or intestines. There is moderate enlargement of the liver. Examination of the lungs, eleven days later, reveals a large effusion on the right pleural cavity, with displacement of the mediastinal contents to the left and a localized area of incomplete consolidation at the level of the third left interspace. The only diagnosis warranted on the radiograph of the lungs is a localized area of consolidation and a large pleural effusion. The new growth element can only be deduced

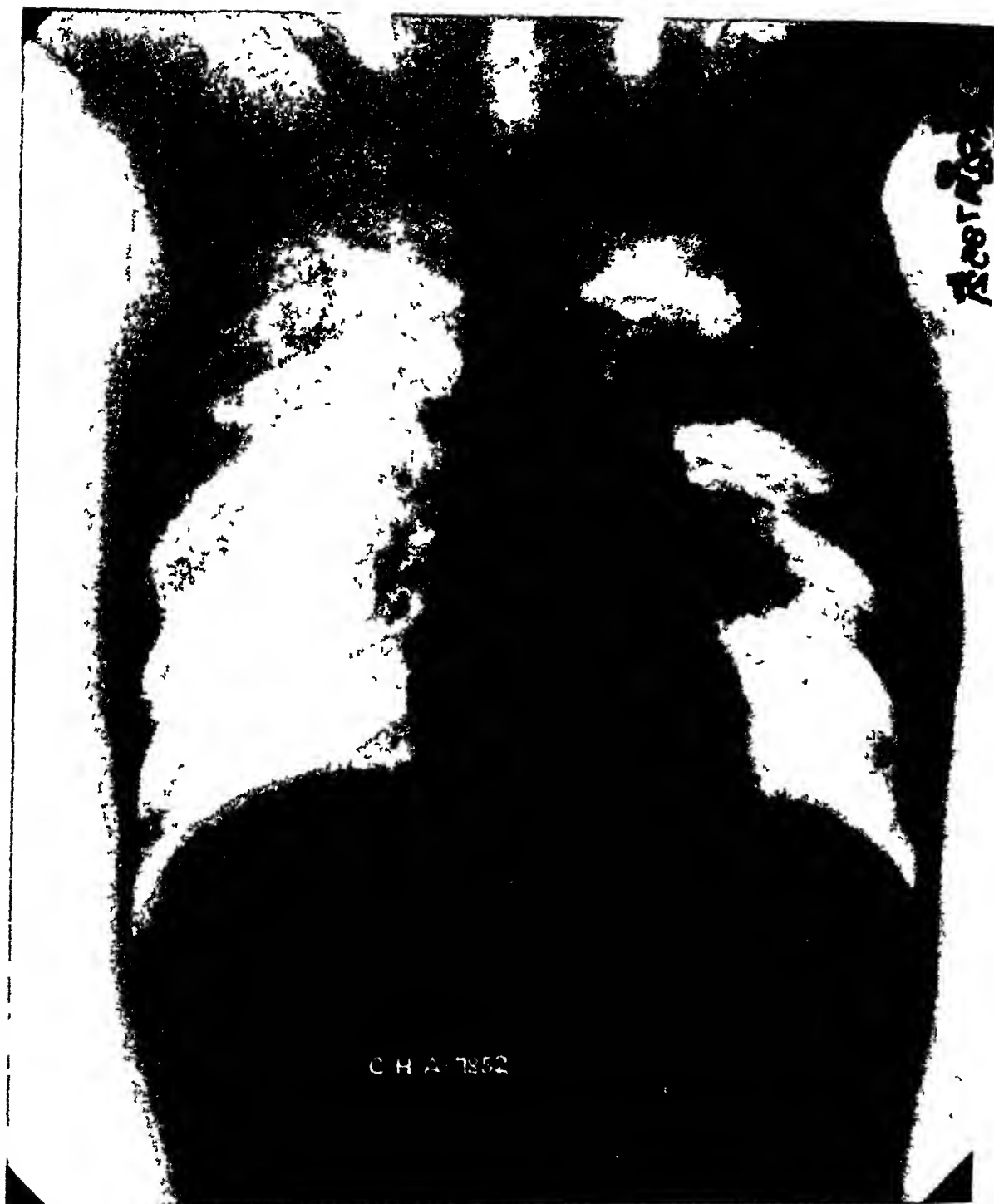


FIG 1 Case III Metastatic tumors in the lung. Numerous well defined areas of infiltration of the parenchyma of various size, spherical in shape, occupy chiefly the upper lobes particularly about the level of the first and second interspaces anteriorly. This is a nodular metastatic neoplastic infiltration from a primary growth in the testicle, diagnosed histologically as embryonal carcinoma.

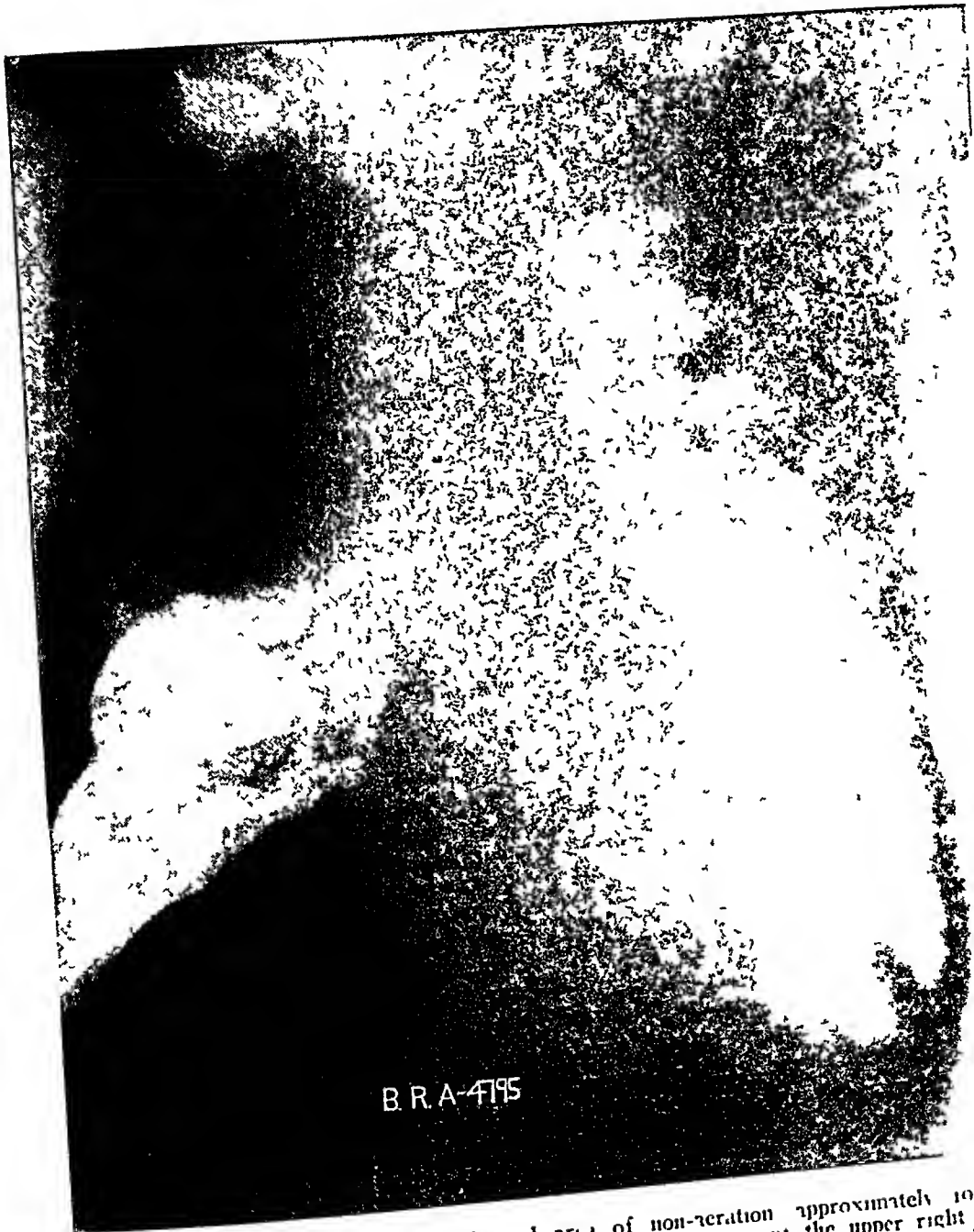


FIG 2 Case IX A large, spherical area of non-aeration approximately 10 cm (film measurement) in diameter, occupies the posterior portion of the upper right lobe. There is no evidence of displacement of the mediastinal contents. There is partial absence of the lateral portion of the second rib probably due to pressure erosion. In pulmonary neoplasm of the primary type in the right upper lobe.

nitely determined by removal of fluid and a re-examination.

The histological findings at autopsy were

Brain Metastatic hypernephroma

Pericardium Metastatic hypernephroma

Lungs. Congestion, edema, anthracosis and metastatic hypernephroma

Right Kidney Hypernephroma

Peritoneum: Metastatic hypernephroma

Vena Cava Metastatic hypernephroma

Case VI Another patient of this type was a woman, No 58893-30, Autopsy No 8704-30, 39 years old, admitted to Kings County Hospital with abnormal pulmonary symptoms, as well as general signs of severe disease. This patient died seven days after admission. A post-mortem examination was made which yielded the following information:

Lungs Metastatic teratoma

Liver Metastatic teratoma

Adrenals Metastatic teratoma

Kidneys. Acute suppurative pyelonephritis

Urinary Bladder Acute gangrenous cystitis

Spinal Dura mater and Posterior Nerve Roots of Upper Lumbar Cord. Metastatic teratoma

Ovary. Primary malignant teratoma

It is not difficult to realize from the histories, that each individual patient with a new growth in the lung can present an interesting problem in diagnosis.

Hamman⁷, of Baltimore, writes "In the lungs, tumor growth may cause cavities, bronchiectasis, erosion of blood vessels, sometimes with fatal hemorrhages, and it may be accompanied by a bronchopneumonia, empyema, abscess or gangrene." He adds, "a small lung tumor that gives no local symptoms may cause widespread metastases, any organ or tissue may harbor metastases, but lymph glands, liver, bones and kidneys are most often invaded." Because of the

variety of the modes of expression of these new growths, the diagnosis of malignant tumor of the lung is not always an easy diagnosis to make.

Case VII A colored man, 46 years old, was admitted to Kings County Hospital and died twenty-five days later. He complained of pain in the right chest, anteriorly, of four months duration, he had a productive cough for six months, with occasionally blood tinged sputum, he had lost thirty-two pounds in weight in five months; he had a marked dyspnea, and complained of extreme weakness. We have presented here the usual symptoms of malignancy of the lung, with the report of a negative Wassermann reaction, and numerous sputum reports negative for tubercle bacilli. He showed signs of serious trouble in the right upper lobe. The radiological report stated "This is a lobar type of lung tumor in the right upper lobe with degeneration and cavitation."

This patient was presented for bronchoscopy. We received the following comment: "Owing to considerable pus and mucus coming from the right bronchus, and also due to the presence of edema of the same bronchus, the examination was not completed. Two weeks after admission, the patient expectorated a red, bloody sputum. Eight days later, he developed a pneumonia in the right lung and died in three days. Clinically this is a patient with a primary carcinoma of the lung, but in the absence of a post-mortem examination, it is impossible to call it primary."

Case VIII A man, No 19143-26, forty-six years old, was admitted to the Kings County Hospital and died fifty-two days later. This patient stated that for the past nine months he had been unable to work because he had not felt well. There were present as complaints: Cough, pain in the chest on the right side, loss of twenty pounds in weight in six months, general weakness, night sweats and anorexia. The patient appeared acutely ill. His temperature was 101.6°, his pulse was 90 per minute, his respirations were 20 per minute. His breath was foul, his mouth contained many carious teeth, the uvula and pharynx were

injected His chest was of the emphysematous type There was dullness on percussion and tubular breathing over the right upper lobe A few scattered râles were heard over both apices The conditions found suggested a new growth in the right upper lobe The radiographic report stated that the picture was suggestive of new growth in the upper lobe, right side Lipiodol injection revealed none of the mixture in the right upper lobe, probably the result of occlusion of the right bronchus, consequent to a new growth The report of a bronchoscopic examination showed that the trachea was found fixed, and pushed towards the left On the right lateral wall in the region of the fourth or fifth tracheal ring there was a small, irregular granulation-like mass about two millimeters in diameter Because of the fixation of the trachea, entrance into the right main bronchus was difficult At the entrance of the upper lobe bronchus, an irregular mass was encountered and a section was removed for examination Microscopic report of the section taken was epidermoid carcinoma

This patient's urine was normal Numerous sputum examinations were negative for the tubercle bacillus His blood Wassermann was negative His blood chemistry showed the following Urea, 40 mg per 100 cc, creatinin, 12 mg per 100 cc, sugar 105 mg per 100 cc

His blood count showed Red blood cells, 3,360,000, hemoglobin, 70 per cent, white blood cells, 15,100, polymorphonuclears, 80 per cent, small mononuclears, 15 per cent, large mononuclears, 2 per cent, transitionals, 3 per cent, morphology, normal

The following interesting comment is made on the history This is a case of malignant tumor of the lung, carcinoma The question of primary or secondary growth must be left to further study by necropsy Unfortunately it was impossible to obtain a post-mortem examination of this patient

Fortunately with the patient whose history I now present, we were granted permission for a post-mortem examination

Case IX A man, No 55210-30, Autopsy No 8668-30, forty-six years old, was admitted to the writer's service at Kings County Hospital complaining of severe, paroxysmal pain in the right chest for seven weeks, cough productive of a whitish sputum, which was blood tinged on two occasions eight weeks and four weeks before admission, loss of twenty-five pounds in weight in six weeks, cyanosis, marked dyspnea upon slight exertion, anorexia since the onset of pain This patient had always enjoyed good health except for an attack of influenza during the epidemic in 1918—twelve years previously At the time of his admission, the patient was in no acute distress, and did not appear acutely ill There was diminished tactile fremitus over the upper right lobe to the fourth rib Dullness on percussion was present over this area, with cavernous breathing and increased whispered voice transmission There were no râles on cough over this area Tenderness was present along the course of the fourth rib, which was roughened in the anterior axillary line While in the hospital, this patient showed mental symptoms, suggestive of metastases to the brain The blood Wassermann was negative Repeated examinations of the sputum were negative for the tubercle bacillus The urine at the time the temperature was 101° showed a trace of albumin, many finely granular and hyaline casts and some leucocytes The blood examination showed red blood cells, 3,468,000, white blood cells, 16,900, polymorphonuclear cells, 75 per cent, small mononuclears, 21 per cent, large mononuclears, 1 per cent, transitionals, 2 per cent, eosinophiles 1 per cent, hemoglobin, 70 per cent

A resumé of the radiographic reports states There is complete consolidation of the upper portion of the right lung the lower level of which is noted at the level of the fourth rib anteriorly, the lower border of this consolidated area is convex downward, the remainder of this lung and the left present no evidence of pathological changes Conclusions—the findings are indicative of pulmonary neoplasm of the upper lobe, right

This patient died nineteen days after admission

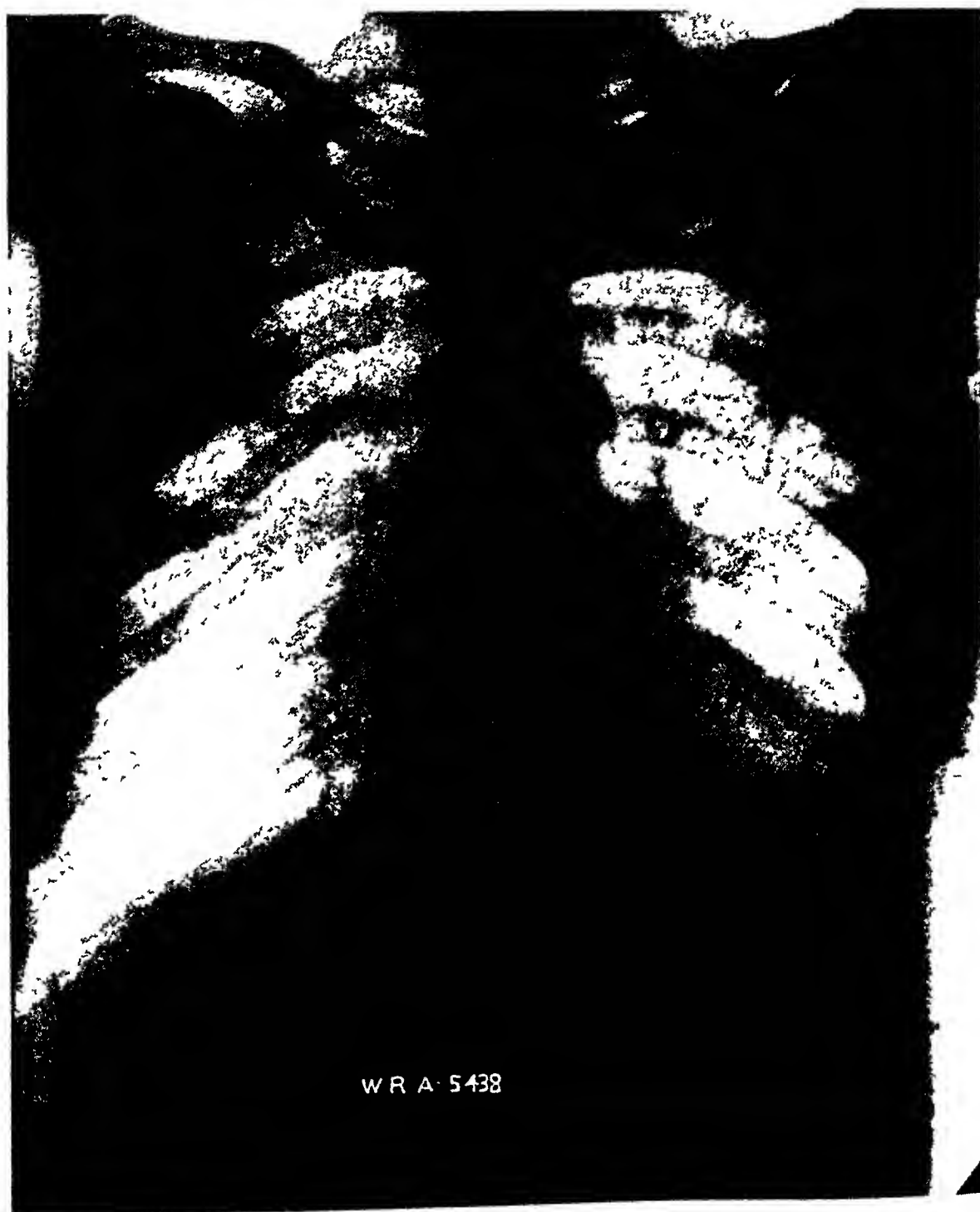


FIG 3 Case X Primary carcinoma of the lower lobe of left lung Consolidation extends almost to the periphery laterally



FIG 4 Case X Primary carcinoma of the lung Bronchography Complete ob-
struction of the lower left bronchus supplying the inner half of the lower lobe

The post-mortem findings were Carcinoma of the lung, primary, right side, congestion of the liver and the spleen, cloudy swelling of the kidneys, congestion and edema of the lungs

Peritoneal Cavity No free fluid, no adhesions

Right Lung Densely adherent to the parietal wall, especially the upper lobe, stripped away with difficulty. There was marked erosion of the 2nd, 3rd and 4th ribs in the mid-axillary line. On section, the upper lobe was found to be filled with a grayish firm tumor mass, in the central portion of which there was a large cavity filled with a reddish cloudy fluid. The lower lobes were dark red and congested, but showed no evidence of tumor.

Left Lung There was some congestion and edema at the base, no enlargement of the mediastinal glands.

Pericardium No free fluid, no adhesions

Histological examination of the lungs showed the presence of a tumor composed of interlacing islands of squamous cells, and here and there occasional attempts at pearl formation. The histologic picture was one of typical epidermoid or squamous-celled carcinoma, and in view of the fact that no other primary focus was observed at autopsy, it is probable that this was an example of primary epidermoid carcinoma of lung, possibly metaplastic. (See figure 2)

Case X Another patient, on the writer's service at the Kings County Hospital, admitted June 18, 1930, was a man, Case No 64670-30, Autopsy No 8831-30, forty-five years old. The patient had noticed for the past year weakness, loss of weight and cough. He had pain in the left chest and shoulder for the past three months, also extreme dyspnea. Physical examination was suggestive of new growth in the left lower lobe, with possibly pleural effusion. No fluid was ever obtained from the pleural cavity. On admission, his blood counts did not show a secondary anemia, his leucocytes were 10,150. An anemia developed later. His blood chemistry was normal. His urine showed a low specific gravity, 1012, a faint trace of albumin, a few hyaline and finely granular casts. The patient remained

in the hospital 152 days before death, expectorated much bloody sputum, had much pain in left lower chest and lost much weight. A résumé of the radiographic report, states: Examination of June 19th, the day following his admission, reveals an irregular area of consolidation occupying the inner and posterior portions of the lower left lobe. No evidence of other pulmonary or pleural pathological changes noted. Approximately one month later, this area of consolidation of the lower lobe, left, is noted to be increased, extending almost to the lateral periphery. (See figure 3)

One week later, bronchography was done by the passive method, at which time there was noted a complete obstruction of the lower bronchus, left, supplying the inner half of the lower lobe (figures 4 and 4A). The occlusion of this bronchus was complete. The remainder of the bronchi extending from the lower main stem were noted to be of moderate size, usual contour and distribution.

Diagnosis New growth, bronchogenic type, of the lower lobe, left.

A bronchoscopic examination made July 31st, 1930, revealed a hard mass obstructing the left main bronchus in the region of the left lower lobe. A specimen of this mass was obtained for examination. A second bronchoscopic examination was made two weeks later, with the findings similar to those of the first examination. The histological report of the biopsy specimen, examined by Doctor Hala, was as follows: The section is one of new growth composed of irregular islands of epithelial cells of the types which are encountered in the two lower layers of the epidermis. The remainder of the section consists of a fibrous stroma with here and there small mucous glands of normal appearance. **Diagnosis** Epidermoid carcinoma.

The post-mortem examination revealed. Emaciation, carcinoma of the lung with involvement of the left bronchus and lower six ribs and dorsal vertebrae, cystic adenoma of the thyroid gland, cloudy swelling of the myocardium, congestion and edema of the lungs, chronic splenitis, moderate passive congestion of the liver, acute nephrosis, atheroma of the aorta, cysts of the adrenals,

adipositas of the pancreas, bronchopneumonia, bilateral pleuritis

At the lower left bronchus, there was found a tumor-like mass with involvement of the left lower lobe throughout. The thyroid was somewhat smaller than normal, on section, the architecture was somewhat distorted and had a shiny appearance. The centre of each lobe was cystic. The lungs were dark gray in color. The pleurae were thickened and adherent throughout both cavities. In the lower left portion of the chest, a tumor-like mass about the size of a grapefruit was found, involving the ribs and vertebrae. These were somewhat soft, friable and undergoing rarefaction. The lungs had a shotty feel throughout. The left lower lobe was entirely made up of tumor and was adherent to the diaphragm. In areas, it was firm, and on section, presented a white, gristly appearance. In other portions of the lung, the appearance was ragged and moth-eaten. The right lung exuded a frothy fluid from the cut surfaces.

The histological data were as follows:

Bronchus The mucosa was absent, and replaced by a tumor consisting of connective tissue stroma and incorporating numerous and irregular islands of epidermal cells.

Left Lung The section showed the presence of a neoplasm which was similar in architecture to that observed in the wall of the bronchus, consisting of numerous islands of epidermal neoplastic cells. There was but little attempt at ultimate differentiation in the tumor cells. In only one area could there be observed an attempt to form an epithelial pearl.

Diaphragm Attached to the diaphragm was a rather large nodule of tumor which in structure resembled that already described in the bronchus.

Aorta Atherosclerosis. The adventitia of the aorta was invaded by nests of epidermal neoplastic cells.

This is evidently a case of primary carcinoma of the lung, originating in the left bronchus. The tumor is definitely of epidermoid structure.

The following history is of interest because it was read at the meeting of

the Brooklyn Society of Internal Medicine on November 28, 1930, as that of a patient with a carcinoma of the lung which we believed to be primary in the lung. This patient died November 28, 1930, and an autopsy was permitted which proved that the carcinoma was primary in the lung.

Case XI A man, Case No. 65352-30, Autopsy No. 8846-30, 50 years old, was admitted to Kings County Hospital July 28, 1930, and died November 28, 1930, after one hundred and twenty-three days in the hospital. He complained of pain in the left chest, cough with expectoration, which was never bloody, weakness, loss of weight and anorexia. These symptoms had been more noticeable during six weeks before admission, although the patient had given up his business, six months previously.

Examination showed the presence of a new growth in the left lung. No masses were found in the abdomen. There were no enlarged glands present. A rectal examination showed no prostatic enlargement. On November 1st, the patient developed a consolidation of the right upper lobe. During the latter part of the patient's stay in the hospital, his expectoration became more profuse and more foul. Three days before death, the following note was made: "The patient coughs considerably and raises much sputum, he has some change in his voice sound. There is a sigh with crack breath, which has a laryngeal quality. He is suffering considerable pain, and has been getting progressively worse." Hemoptysis was never present during his stay in the hospital. Repeated examinations of his sputum were negative for the tubercle bacillus. His blood Wassermann was negative. His urine showed the following:

Specific gravity, 1012, faint trace of albumin, occasional hyaline casts. Blood Chemistry—Urea, 20 mg per 100 cc of blood, creatinin, 1.1 mg per 100 cc, sugar, 100 mg per 100 cc.

His blood on admission was: Red blood cells, 4,448,000, white blood cells 5700 polymorphonuclear cells 68 per cent.



FIG. 4A. Case X. Bronchography. Primary carcinoma of lower left bronchus
Oblique position

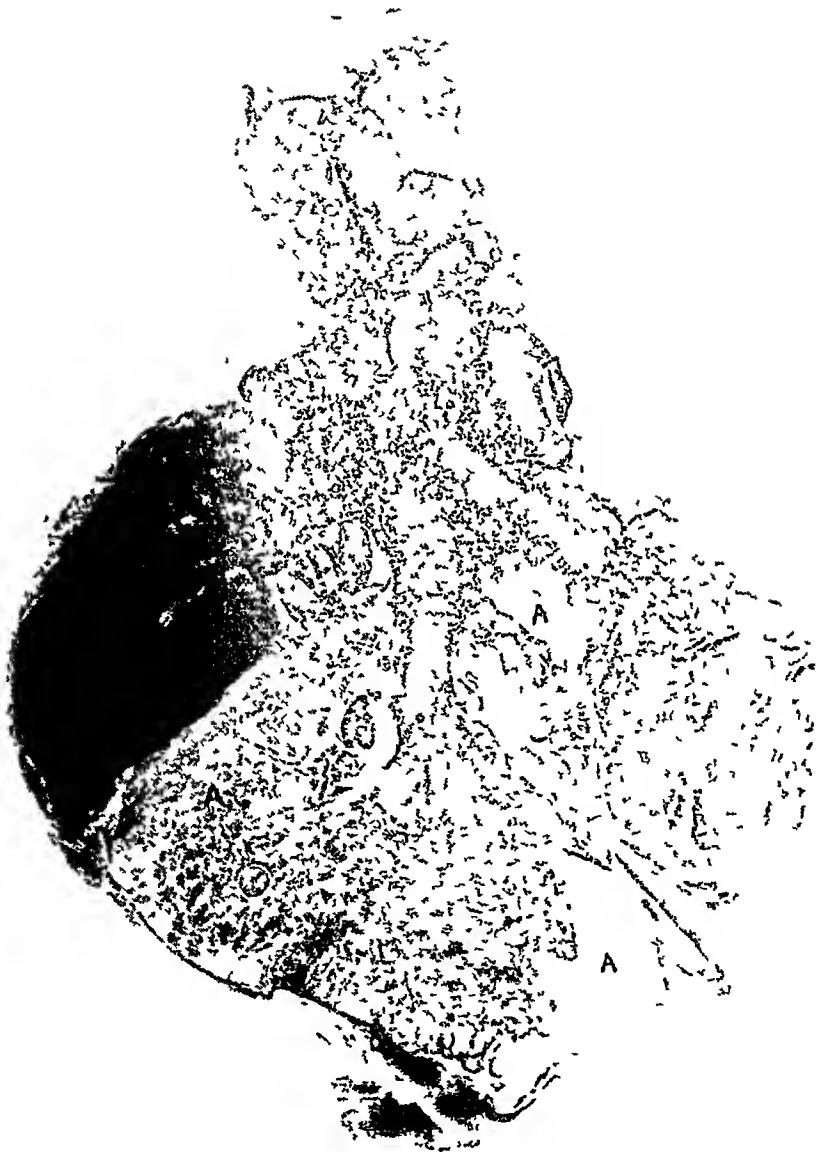


FIG 5 Case X A bronchogenic tumor whose origin is just at the bronchial bifurcation (see arrow) At A are seen secondary tumor masses in the pulmonary parenchyma

hemoglobin, 80 per cent, morphology, normal

A résumé of the radiographic reports states: There is a slight decrease of aeration of practically the entire upper lobe, left, with a moderately large mass of irregular contour at the left hilus. In the posterior portion of the lower lobe is seen a horizontal fluid level, which is indicative of a partially filled abscess cavity. Examination of the osseous system at this time revealed no tumor growths in the bones. Examination three months later revealed no further decrease of aeration of the upper lobe, left, and a partial decrease in the lower lobe, the mass at the hilus has increased in size and in its outer portion is an irregular area of re-aeration indicative of partial destruction (degeneration) of this process. Conclusions: A primary new growth of bronchogenic type with partial obstruction to the aeration of the left upper lobe and infection with abscess cavitation in the left lower lobe as described, and probable degeneration of the neoplastic mass in the upper lobe.

A report of the bronchoscopic examination follows: Direct laryngeal examination reveals a complete paralysis of the left vocal cord with partial involvement and limitation of the right vocal cord. Examination of the bronchi reveals an extensive growth involving the left main bronchus, including the corina and extending to the right bronchus (posterior left lateral aspect). A specimen of the tumor was taken for microscopic study. The report upon this specimen is that "this section shows a portion of tumor growth which is composed of numerous islands of squamous epithelial cells. Mitotic figures are present. Diagnosis: epidermoid carcinoma."

Upon the death of the patient, permission was obtained to perform a post-mortem examination, which revealed:

Primary carcinoma of the left lung with involvement of the lower six ribs on the left side and the corresponding vertebrae, acute nephrosis, vascular nephritis, chronic myocarditis, congestion and edema of the lungs, bilateral pleuritis, abscess of the lung, left, moderate passive congestion of the liver, acute splenitis, general arteriosclerosis, adiposis of the pancreas, emaciation

The body was that of an elderly male about fifty-five years old, rigor present, lividity absent, emaciated and dehydrated with the supra- and infra-clavicular depressions marked.

Upon removal of the sternum marked bilateral pleuritic adhesions were found. The omentum was attached in the gall-bladder region beneath the liver. The left lung adhered to the posterior wall of the thorax especially in the region of the lower six ribs and corresponding vertebrae. The lung was freed and a solid tumor mass was found involving the lower lobe in its posterior aspect, and in the anterior aspect, an abscess cavity was noted. The corresponding ribs and vertebrae showed rarefaction of bone. The right lung was rather shotty on palpation. The pleura was thickened, and on section, a small amount of frothy fluid could be expressed. No tumor could be noted in the right lung, but the peribronchial lymph glands were markedly enlarged, and also, extending down from the bifurcation of the bronchus, a tumor-like mass was noted having a fungus-like appearance. The entire left lung showed consolidation except at the upper portion of the lower lobe which contained an abscess cavity about the size of a lemon. Dissection of the bronchus of the left side shows neoplastic infiltration which began about 0.75 cm above the bifurcation and continued down about 2.5 cm into the left bronchus. At the terminus of the bronchus on the left side, was an abscess cavity. The lung on section showed this circumscribed cavity, and also a tumor-like mass involving the upper and lower lobes, with thickening of the pleura.

Histological data —

Heart: Marked adiposis, cloudy swelling of myocardium.

Lungs: Epidermoid carcinoma. The tumor cells, in general, are squamous in morphology and are surrounded by fibroblastic tissue. The section incorporates part of the bronchus which latter shows evidently the primary focus.

Liver: Cloudy swelling, moderate chronic passive congestion.

Spleen: Congestion and edema.

Adrenals Cloudy swelling, congestion and edema of medullae
 Pancreas Moderate adiposis
 Kidneys Cloudy swelling
 Aorta Calcification of media

Cause of Death Primary carcinoma of the lung, with involvement of the lower six ribs and corresponding vertebrae

On January 24, 1931, a short time before the preceding section of this paper was prepared, a patient, M N, a woman 52 years old was admitted to Kings County Hospital with the following complaints—Cough of four months' duration, with slight expectoration, not bloody, pain in the left chest, loss of weight, fourteen pounds in four months, dyspnea, of two months' duration, increasing in severity, no night sweats

One month before admission, the patient developed what she called a "fresh cold," which persisted. For the past two months, the patient slept only on the left side because of increase in cough and dyspnea in any other position. On admission, the patient was not emaciated, did not appear acutely ill, was not suffering severe pain, but had a marked dyspnea.

Physical examination revealed the signs of an effusion in the left pleural cavity and, possibly because of the recent review of the subject, the resident physician made the additional diagnosis of malignancy in the lung.

Thoracentesis was performed twice, five days after admission, 1500 cc of a clear, serous fluid was withdrawn, and eleven days after admission 1250 cc of a dark amber fluid. Both fluids under the microscope showed many red blood cells and were transudates.

Examination of the blood on admission showed

Red blood cells, 3,808,000, white blood cells, 12,200, polymorphonuclear cells, 70%, small mononuclear cells, 25%, large mononuclear cells, 3%, transitional cells, 1%, eosinophilic cells, 1%, hemoglobin, 80%

Blood Chemistry—Urea, 30 mg per 100 cc of blood, creatinin, 12 mg per 100 cc, sugar, 145 mg per 100 cc

Examination of the urine showed no abnormalities. Sputum examination was negative for the tubercle bacillus. Blood Wassermann was negative. Six days after ad-

mission, blood streaked sputum was present and there was a sharp rise in temperature. During the stay in the hospital, the temperature varied between 99.8° and 104.4° and never became normal. The dyspnea increased in severity, cyanosis was marked and the patient showed an increasing heart impairment. On the seventeenth day in the hospital, an erysipelas developed on the left side of the head and face, the temperature rose to 103°, the pulse to 124, and the respiration became 32. Signs of a bronchopneumonia were present. Radiographic reports taken on admission and later were "massive effusion of the pleural cavity." Twenty-one days after admission, the patient died, apparently from cardiac involvement.

The findings on post-mortem examination were unusually instructive. They revealed

Congestion and edema of the lungs, bronchopneumonia, primary bronchogenic carcinoma on the left side, bilateral pleuritis, chronic myocarditis, atheroma of the aorta, acute and chronic pericarditis, passive congestion of the liver, septic spleen, chronic vascular nephritis, degenerated adrenal, chronic fibrotic oophoritis.

Marked bilateral pleural adhesions were found. In the left thoracic cavity about 100 cc of cloudy, gray, thin fluid was present, and a fresh, fibrinous plastic exudate surrounded the entire lung and upper surface of the diaphragm. The right cavity showed a similar plastic exudate and a moderate amount of transudate fluid also. The pericardium was adherent to the left lung and occupied about twice the normal space in the mediastinum. The lungs weighed 1800 gms.

The left lung was of a grayish white color. A firm, tumor-like mass had invaded the lower portion of the upper lobe and the major portion of the lower lobe and in an area about the diameter of a silver dollar had extended into the visceral pleura. The trachea and bronchi which were dissected out with the lungs were incised and inspected and the tumor-like growth found to have begun, apparently about one-half inch below the bifurcation in the left bronchus, showing a line of demarcation which was pale, anemic and irregular.

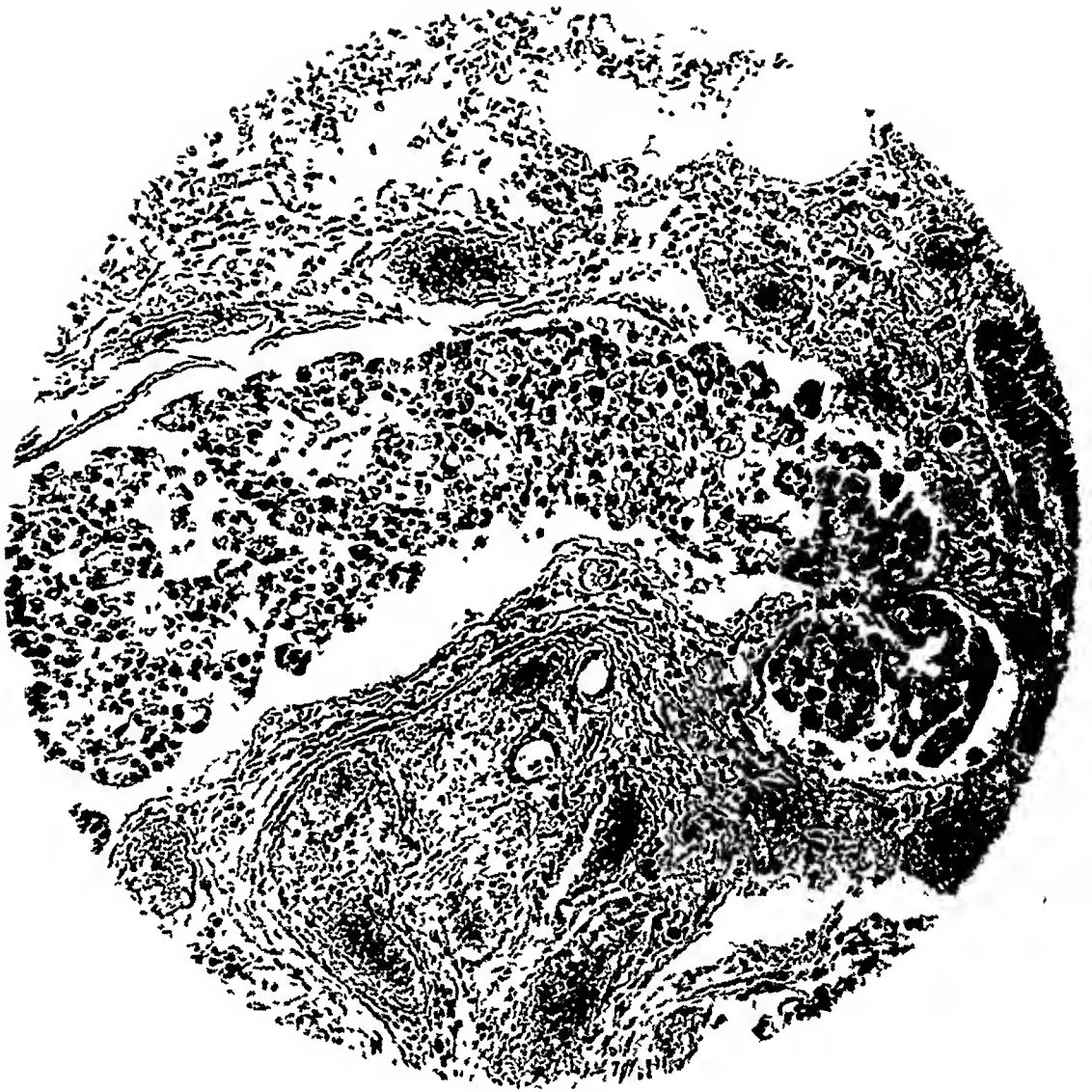


FIG 6 Case X A primary carcinoma of the lung of the epidermoid type with origin just at the tracheal bifurcation, (see figure 5) At the right is seen the lumen of a normal bronchiole

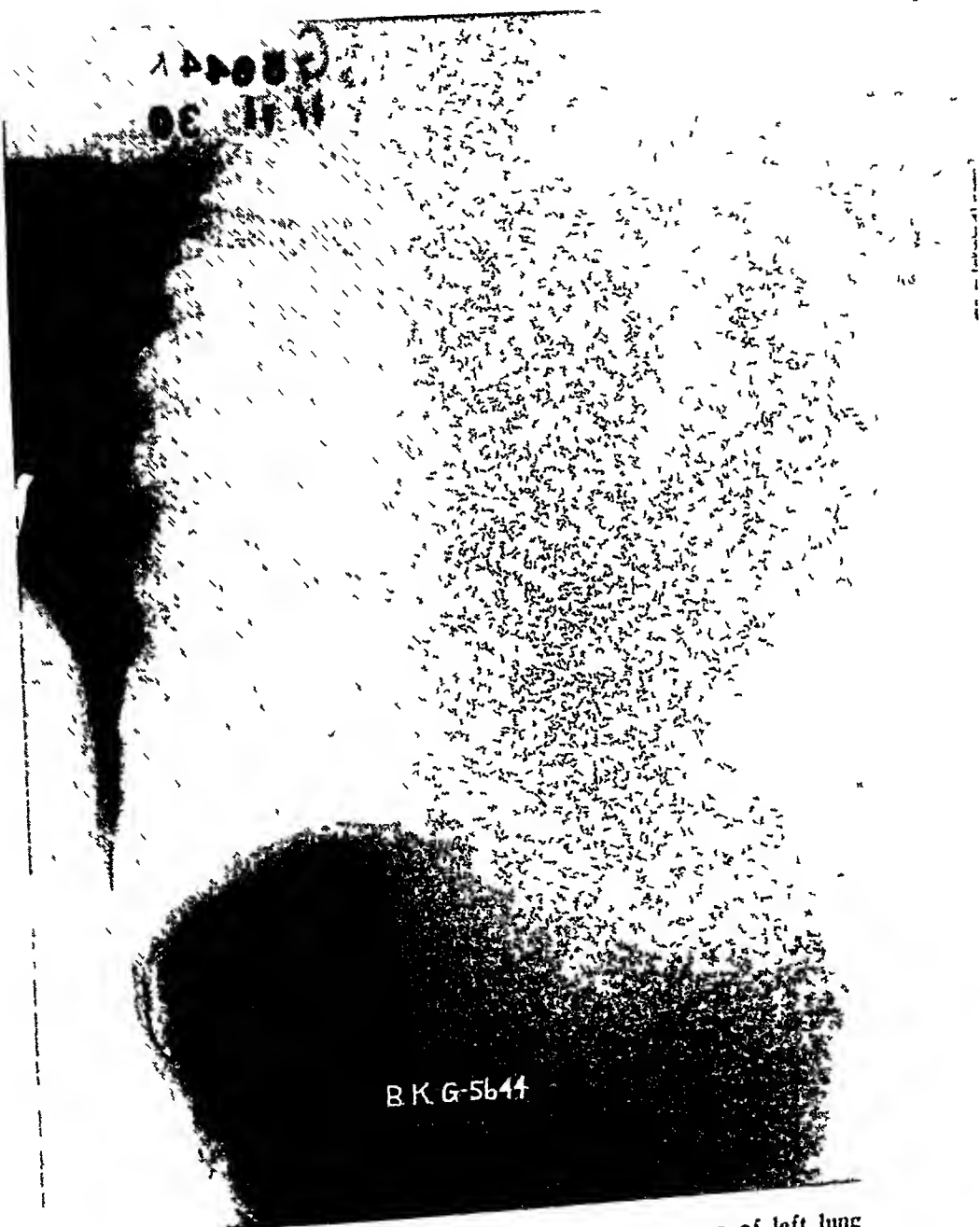


FIG 7 Case XI Primary bronchogenic carcinoma of left lung

trast to the normal tissue. The left lung on section, presented a pale, grayish growth, indurated in character and occupying the portions of the lobes above mentioned. The peribronchial lymph nodes were also involved, being enlarged, firm and fibrous.

The right lung was dark gray in color with no apparent metastases. On section, there was a patchy consolidation in the lower lobe showing grayish, granular areas. A frothy fluid could be expressed from the other lobes. The pericardium was thickened and adherent to the left lung, also to the epicardial surface giving the appearance of "bread and butter," the cor villorum or hirsutum, especially over the left ventricle. In the region of the right ventricle, old fibrinous strands were present. The visceral layer of the pericardium was hemorrhagic and injected.

The heart was markedly enlarged, weighing 600 gms. The ventricular walls were thinned out and of light brown color. On section, fibrosis was present in the musculature. The mitral leaflets were somewhat thickened along their free borders, the aorta showed raised atheromatous plaques, the coronaries were narrowed.

The cause of death was Primary bronchogenic carcinoma of the left lung.

Histological examination confirmed the findings of primary carcinoma of the lung, together with bronchopneumonia, acute seropurulent epicarditis, chronic fibroblastic pericarditis, acute seropurulent pericarditis, facial erysipelas.

It is a privilege to present here for the first time, the histories of five patients with primary carcinoma of the lung proven by autopsy. These five, together with the three reported in detail by the writer⁸, in 1925, make a series of eight cases of primary carcinoma of the lung at the Kings County Hospital since February, 1924, three in 1924, and one in 1927, and the four last mentioned within the past six months. We feel that a number diagnosed as carcinoma of the lung, upon which no autopsies were permitted,

were primary growths in the lung, the four patients whose histories have just been given were diagnosed as carcinoma before death and the primary condition was proven when post-mortem examination was allowed.

In making a diagnosis, the following steps are taken. The history, the physical findings, the course of the disease, and as at the time of Graves' lecture, the gross findings of tumor at autopsy. To these findings have been added

- (1) The fluoroscopic examination and the roentgen ray picture,
- (2) The bronchoscopic examination and the microscopic examination of the specimen obtained during life,
- (3) The histological findings at autopsy.

The use of the bronchoscope has been of inestimable value as an adjunct in diagnosing these malignant conditions.

"The value of bronchoscopy in diagnosis is primarily dependent on data obtained by direct visual inspection. It must be remembered, however, that in a diagnosis of pulmonary disease, the entire lungs are not open to inspection. Only the larger bronchi can be examined. The minute branches cannot be inspected by any endoscopic means. However, secretion can be observed coming from the orifices of the small branches and uncontaminated specimens of this can be removed for bacteriological study. Positive findings are of the utmost value. Bronchoscopy is indicated when there is a diagnostic question remaining after physical examination, radiographic studies and laboratory investigations have been carried out⁹."

In reviewing eighty-one histories of patients at the Kings County Hospital, presenting evidence of malignant tumors in the lung, the writer found pa-

tients who may be classified as follows

Eight with primary carcinoma in the lung

Thirty-five with what is believed to be carcinoma in the lung, without autopsy, and not metastatic from other organs

Twenty with metastatic carcinoma in the lung

Ten with metastatic lymphosarcoma

Six with metastatic sarcoma

One with metastatic hypernephroma

One with metastatic teratoma

Primary sarcoma in the lung is rare. Carcinoma is the commonest tumor in the lung, whether primary or secondary. These secondary growths may occur by direct extension from contiguous carcinomata, or as metastases from distant tumors. Pleural effusion is usually the first evidence of direct invasion from the breast or the stomach. Of carcinomata that metastasize to the lung, breast and kidney tumors are clinically the most important. These metastases are frequently small, and even though they may be numerous, they may cause few pulmonary symptoms, and are usually overlooked clinically. Occasionally miliary carcinomatosis of the lung occurs. The association of obscure or unusual pulmonary symptoms and signs with one or more nodules in the bones is peculiarly characteristic of hypernephroma, although it may be present in sarcoma.

From the histological viewpoint three types of pulmonary carcinoma are recognized, arising respectively from the bronchial epithelium, the

bronchial mucous glands, and the alveolar epithelium. In other words, they may be bronchogenic or parenchymal.

Carcinoma arising from the bronchial epithelium often causes bronchial obstruction and bronchiectatic cavities, it seldom causes a diffuse tumor of the lung.

Carcinoma arising from the mucous glands begins in the large bronchi. A number of small growths have been described of glandular structure with mucous secretion beginning in the walls of the bronchi, and covered by intact bronchial epithelium. These typical mucous gland tumors infiltrate the bronchial wall, often causing bronchial obstruction. As the tumor spreads by direct growth and by metastasis, the characteristic gross and histological picture may become obscured. The secretion of abundant mucus is a very characteristic feature of mucous gland growths, although it is not restricted to them.

Carcinoma arising from the alveolar epithelium produces infiltrating masses which often spread rapidly, involving a lobe or larger areas, and somewhat resemble organizing pneumonic consolidation. At times, instead of a diffuse growth, multiple nodular tumors are formed.

Secondary sarcoma of the lung is less common than secondary carcinoma, although melanotic sarcoma and sarcoma of the bone almost always metastasize to the lungs. Pulmonary lympho-sarcoma must always be secondary to tumors arising in lymph glands or in the thymus.

"General weakness is a frequent complaint, often an initial one, and it increases as the disease progresses but is not



FIG 8 Case XI Primary carcinoma of the lung This neoplasm is bronchogenic in origin and its focus can be seen readily at the bifurcation of the trachea just above A The mucosa of both bronchi is infiltrated for some distance below the bifurcation and at A the tumor has advanced into and through the bronchial wall Secondary nodules are exhibited at B The arrow points to a large bronchiectatic cavity There is considerable thickening and invasion of the visceral pleura at C

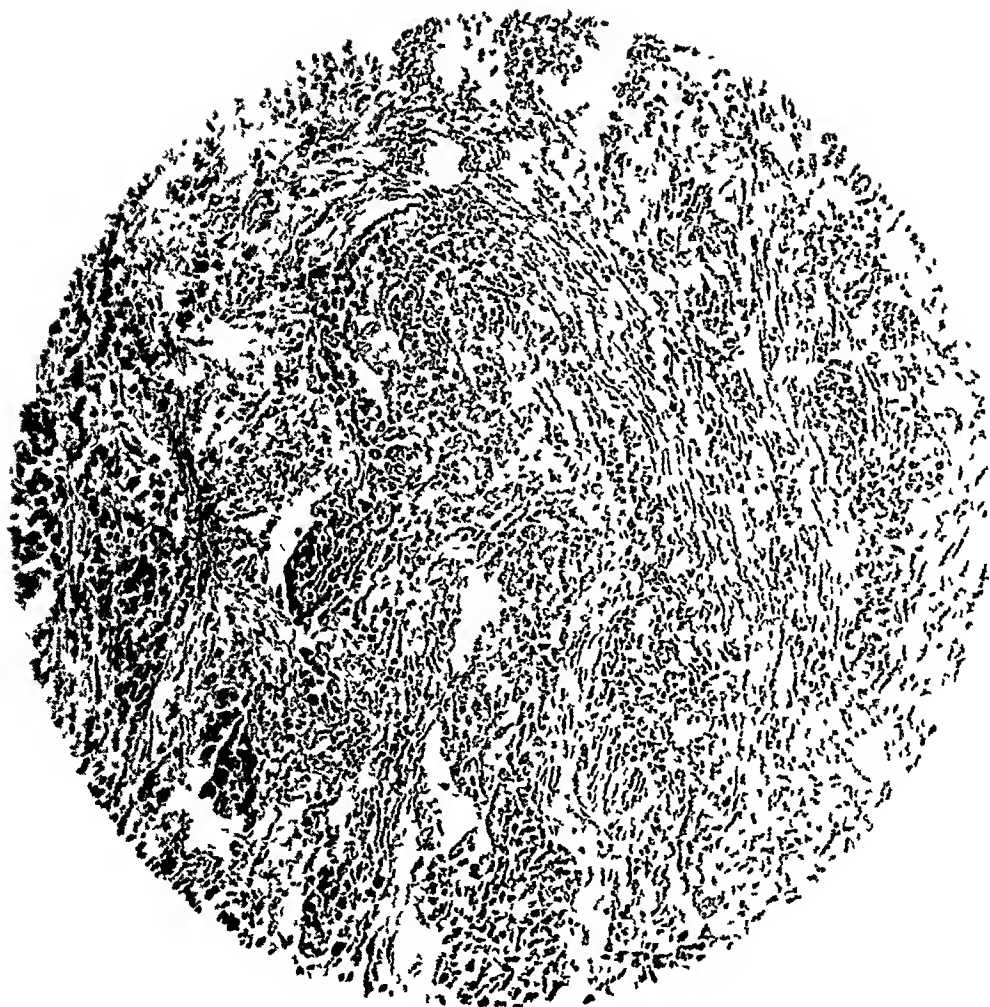


FIG 9 Case XI Primary carcinoma of the lung This section shows an epidermoid type of growth in the lung parenchyma There is considerable fibroblastic stroma The primary growth in this case is illustrated in figure 8

ing is by no means a constant occurrence in malignancy of the lung. In some patients, however, the onset of manifest symptoms is slow and insidious. In a number of patients, the first serious manifestation of disease occurs with comparative suddenness. The patient may seek the physician

(1) primarily on account of hemoptysis, the cause of which has either not been determined, or has been thought erroneously to be tuberculosis of the lungs,

(2) because of evidences of pleurisy with or without effusion,

(3) those whose history and physical examination suggest the presence of a localized infection within the chest,

(4) those suffering from grave disability and showing the more obvious phenomena which characterize the later stages of intrathoracic malignant disease".⁵

In regard to the presence of pleurisy, we feel that the commonest cause of pleurisy in the young adult is tuberculosis. We also feel that we must always keep in mind that the occurrence of an unexplained pleurisy, especially of a pleurisy with effusion, in a patient of middle age or later, should suggest the question of the presence of new growth in the lung or mediastinum. If the effusion is bloody, it may be regarded as almost pathognomonic of malignant disease in the lung or pleura. The presence of tubercle bacilli in the sputum does not exclude malignancy of the lung, which may co-exist with pulmonary tuberculosis. A malignant tumor may be present in the lung of a patient having syphilis, and one has to make a differential diagnosis between gumma of the lung and a non-syphilitic tumor.

No brief description of the physical signs can be given. These must differ according to the type of the disease, the site of the tumor, the extent of lung involved, and the presence or ab-

sence of effusion in the pleural cavity.

As we may see from the histories of these patients, the commonest signs and symptoms are

Cough with or without expectoration, which, if present, may be bloody

Hemoptysis,

Dyspnea—very severe in some cases,

Pain—which may be steady or paroxysmal,

Cyanosis,

Weakness,

Emaciation—which is not always present,

Gastric symptoms—which may be present but are not common,

Fever—which may be present in moderate degree, due to secondary illness

What may we consider the prognosis in these patients with malignancy of the lungs? The general rule in all malignancy—"the earlier in life that the growth appears, the more malignant it will be," seems at present to be our answer.

The mode of death may vary in different individuals. There may be a gradual general failure. Death may result from sudden, large hemorrhage, this is considered rare. The patient may have a hemiplegia due to metastasis lodging in one of the cerebral vessels and causing embolism. He may lapse into coma due to a growth in the brain tissue, more often the coma is due to a toxic state, with a general septic absorption. There may be sudden and distressing dyspnea with death.

What should be our feelings concerning the treatment and the results

of treatment in these severe conditions? When one considers that the treatment of malignancy seems now as hopeless as did the treatment of pernicious anemia when many of us began the study of medicine, we should be hopeful of developing a cure in malignancy. How wonderfully, indeed, has the prognosis in pernicious anemia been changed by the use of liver and defatted stomach in treatment^{10,11}. Surely, we must be encouraged, also, by the advance in the methods of treatment of many of the scourges of the world, such as the use of quinine as a specific in malaria, the vaccine for small-pox, antitoxin for diphtheria, anti-tetanic serum in the prevention of tetanus, typhoid and paratyphoid vaccine in the prevention of typhoid and paratyphoid fevers, and meningococcic serum in the treatment of meningococcic meningitis. Something must and will be found to combat successfully every malignancy wherever it may be found in the body. The surgeons feel that surgery may be of benefit where it is possible to discover the condition early. Electrical treatment, and possibly radium, may be the means by which this seemingly hopeless problem will be solved. The cure may be accomplished before the cause of malignancy is discovered.

I wish to acknowledge here my appreciation to my colleagues at the Kings County Hospital in all departments of the Hospital for the cordial co-operation accorded to me in reviewing this work. Doctor Rendich, Director of the Radiographic Service, has kindly read the radiographic pictures, and Doctor Hala, Director of the Pathological Service, has kindly translated the pathological slides, the Record Room Service has been invaluable in correlating this review.

Without this co-operation, it would have been impossible to have completed this agreeable task.

SUMMARY

A study of eighty-one patients with malignant tumors in the lung presented —

Eight with primary carcinoma in the lung, confirmed by autopsy,

Thirty-five believed to be carcinoma in the lung, the diagnosis having been made on the history, physical examination, radiographic findings and bronchoscopy with biopsy specimen but without autopsy,

Twenty with metastatic carcinoma in the lung from a primary focus elsewhere,

Ten with metastatic lymphosarcoma in the lung,

Six with metastatic sarcoma in the lung,

One with metastatic hypernephroma in the lung,

One with metastatic teratoma in the lung,

It has been possible to demonstrate and illustrate in this paper every step in arriving at the diagnosis of primary carcinoma in the lung.

Of the eight primary carcinomas in the lung, all were found to be unilateral, with four involving the right lung and four involving the left lung. The symptoms presented by these eighty-one patients varied according to the stage of the disease, the type of tumor, the site of the tumor, the amount of lung tissue involved, and the presence or absence of effusion in the pleural cavity. The commonest symptoms were cough, with or without expectoration, which, if present, was usually bloody at some period of the

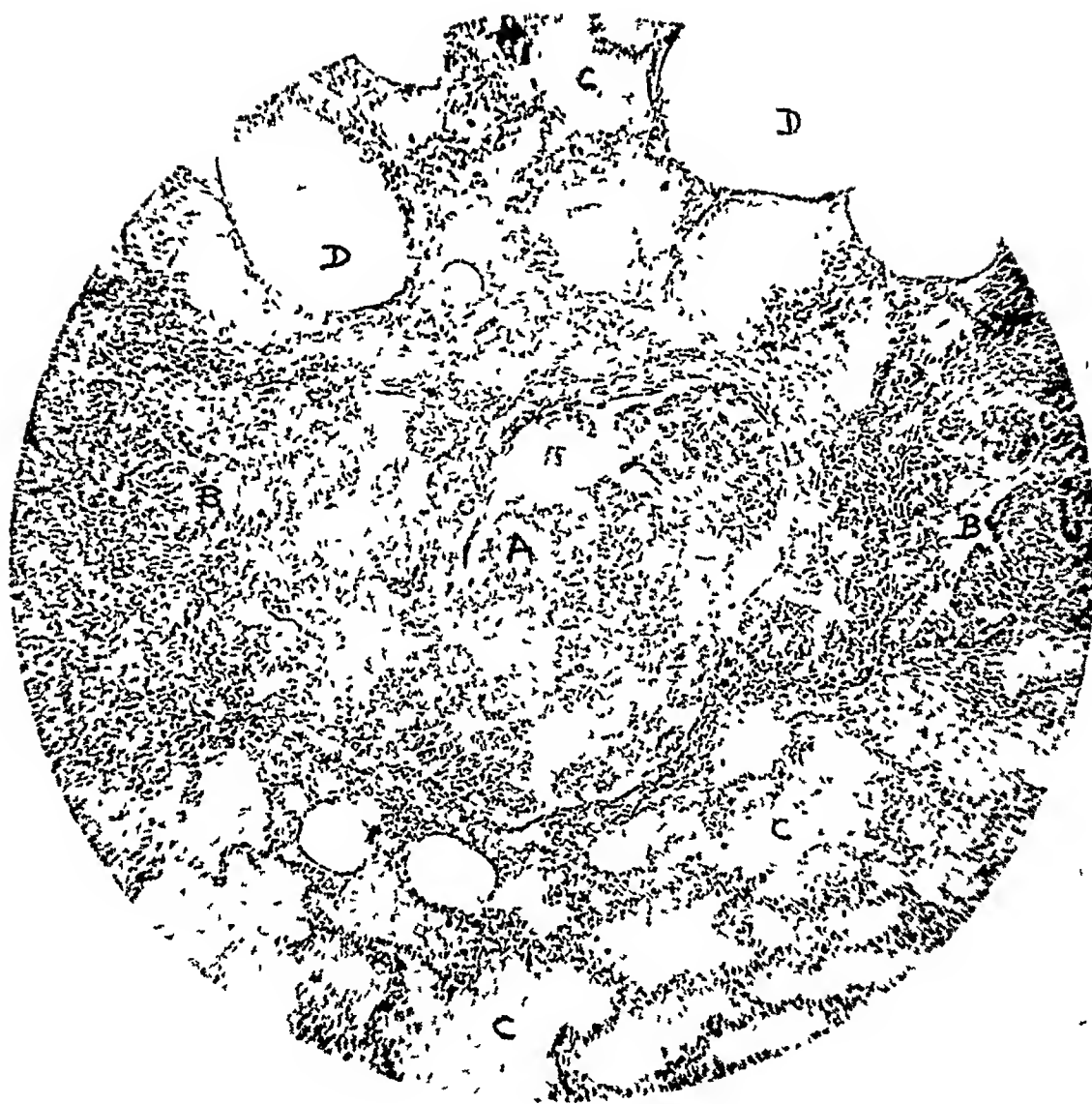


FIG 10 Case XI Primary carcinoma of the lung This tumor is definitely adenomatous in architecture as is well shown at A This is a type which is bronchogenic in origin and undoubtedly derived from the submucosal glands of a bronchus In the lower part of A, the cylindric epithelium is well demonstrated The growth has a tendency to be papillated at B Edematous alveoli are found at C, and compensatory emphysema at D



FIG 11 Adenomatoid changes in the lung This section is from a patient having pulmonary syphilis and illustrates the possibility of neoplasia secondary to a luetic lesion. A group of gland-like spaces is seen at A. They are lined by cubical cells. At B is a small miliary gumma, while fibroblastic tissue (an example of the productive inflammation unfailingly observed in lues) can be seen at C.

disease; dyspnea, pain, cyanosis, weakness, emaciation. Hemoptysis was present in those patients having blood vessels involved in the tumor, with ulceration. Fever may be present in the early stages in the presence of a pneumonitis which is usually diagnosed as an atypical pneumonia which does not resolve completely, in the later stages, fever is present because of an inflammatory process in and about the tumor. Abstracts of the histories of eleven patients are given, illustrating these conditions. The post-mortem findings are reported with nine of these histories.

Secondary growths in the lung show an advanced condition of malignancy in the body, and although electric treatment may ameliorate the symptoms and prolong the patient's life, not a great amount of benefit is believed to result from the present treatment of these secondary conditions.

In primary cancer of the lung, in order to diagnose the condition earlier than is usually done, it is necessary that we concentrate our attention (1) upon those patients who complain of persistent cough without demonstrable causes; (2) upon those patients who expectorate bloody sputum at intervals, with no tubercle bacillus in the sputum, (3) upon those patients who complain of general weakness, loss of weight, and do not react to the usual methods of treatment. The value of post-mortem examinations is demonstrated here, and our constant effort should be to obtain permission for more of these examinations. We must be hopeful in the not too distant future for cure of these malignant conditions, as the slight benefit from electrotherapy may be the forerunner of methods to inhibit and stop the destruction of life by these "outlaw" growths.

REFERENCES

- ¹GRAVLS, R. J. Clinical lecture on the practise of medicine, Vol II, p 70, 1884, The New Sydenham Society, London
- ²MORGAGNI, G. B. De sedibus et causis morborum per anatomen indagatis, 3v, 1779, Ebroduni in Helvetia
- ³ADLER, I. Primary malignant growths of lungs and bronchi, p 17, 1912, Longmans, Green and Company, New York
- ⁴ROSAHN, P. D. Incidence of primary carcinoma of lung, Am Jr Med Sci, 1930, clxxxix, 803-811
- ⁵DAVIDSON, MAURICE. Cancer of the lung and other intrathoracic tumors, p 42, 1930, William Wood and Company, New York
- ⁶EWING, JAMES. Neoplastic diseases, p 857, 1928, W B Saunders Company, Philadelphia
- ⁷HAMMAN, LOUIS. Diseases of the lungs, The Oxford Medicine, Vol II, Part I, Chapter III, p 82, 1920, Oxford University Press, New York
- ⁸MOSES, H. M. Primary carcinoma of lung, Am Jr Med Sci, 1925, clxx, 102-118
- ⁹NORRIS, G. W., and LANDIS, H. R. M. Diseases of the chest and principles of physical diagnosis, p 340, 1929, W B Saunders Company, Philadelphia
- ¹⁰RIDDLE, M. C., and STURGIS, C. C. Effect of single massive dose of liver extract on patients with pernicious anemia, Am Jr Med Sci, 1930, clxxx, 1-11
- ¹¹STURGIS, C. C. and ISAACS, R. Treatment of pernicious anemia with desiccated defatted stomach, Am Jr Med Sci, 1930, clxxx, 597-602

The Dietetic Treatment of Tuberculosis*†

By ERNEST S. MARIETTE, M.D., F.A.C.P., *Oak Terrace, Minnesota*

IN a previous article the writer has discussed this subject from the administrative standpoint. This discussion will include a broad outline of early history of food supply and diets and its effect upon early medical opinion in the attempt to show how these factors have influenced man's ideas concerning the importance of diet in tuberculosis. While there is still a wide difference of opinion as to the most valuable diet in tuberculosis, an attempt will be made to outline a sane and reasonable basis for the diet used at Glen Lake Sanatorium. Although it is realized that an improvement in nutrition alone may have no effect on the tuberculous lesion, we still believe that every effort should be made to improve the nutrition of the patient, so that his resistance to infection in general may be increased and his sense of well-being improved.

The importance of diet in the treatment of tuberculosis has as its background all of the weight of economic and medical history. Until comparatively recent times the common man has suffered from an unsatisfied hunger. For instance, in the times of the Greeks and the Romans a three pound

mullet cost the equivalent of seventy to eighty dollars in today's money, and at one time Domitian ordered a special session of the Senate to determine the best way to cook a turbot. Surely ancient man loved his food and its palatability was of great importance to him. In the time of Queen Elizabeth only about one-half of the common men had fresh meat as often as once a week and the other half never tasted it at all, and in the time of Louis XV a pound of sugar cost sixty to eighty francs. Therefore, about all that was available for the poor man was bread, peas, soup, bark of trees and certain raw vegetables which are now recognized as very important articles of diet but which were formerly scorned by the wealthy man because of their low cost and common use. These raw vegetables were also believed to be indigestible and harmful "if not by doctor's prescription or their evils lessened by cooking." "The medieval cuisine consisted chiefly of soup and soup meats and the exceptions to this rule were few."

Man's struggle for his bite to eat must have made an indelible impression on his mind. He was often tired, hungry and thin and if by chance he secured an adequate amount of food he immediately felt well and strong again. This fact, together with

*From Glen Lake Sanatorium, Oak Terrace, Minnesota, and the Department of Medicine, Medical School, University of Minnesota.

†Received for publication, April 30, 1931.

the fact that man's diet has varied with the locality, the climate and the soil, and the proximity to large bodies of water without any markedly different effect upon his mental or physical development must have indicated to the physicians, at least, that the quantity of food was of much more importance than its character.

Early medicine developed about the diet and the care of the gastrointestinal tract and the patient "went to the same professor for physic and food" Therefore, it was only natural that Hippocrates, Galen, Morten, Reed, Bayle, Laennec and numerous other physicians and writers should all stress the importance of diet in the treatment of any disease such as tuberculosis which is characterized by loss of weight and strength. So much attention was paid to the palatability of the food in the hope that the patient's appetite would be stimulated and thus compensate for the loss of weight, that "a culinary recipe was often considered a remedial prescription"

While the idea of the importance of diet in the treatment of tuberculosis was based on an inaccurate knowledge as to its cause, nevertheless this apparently logical treatment has become so firmly entrenched in the therapeutics of the professional and lay worlds that many still cling to it. In 1835 Clark called attention to the danger of over-feeding the patient, "by which the stomach and bowels are disordered and a new train of symptoms produced which complicates the case and adds to the patient's distress" He also claims that "abdominal congestion leads to a similar condition of the lungs and under such conditions the

patient's life is in imminent danger" This is an actual paraphrase of a statement made centuries before by Hippocrates. Kiamet, Grayzel and Shear say that in the olden literature as reviewed by Wells, DeWitt and Long, cod liver oil is mentioned frequently as having great value in the treatment of tuberculosis. Williams, in the early part of the 19th century, claimed that in his opinion "cod liver oil had done more for tuberculosis than all other measures put together" We now realize that its value is probably due to its vitamin content. Unfortunately some people have such a low fat tolerance that they are unable to use cod liver oil and the vitamin content varies with the quality of the cod liver oil. Even as late as the early part of this century, the treatment of tuberculosis consisted of fresh air and an attempt to over-feed the patient. Instances are on record of patients attempting to consume—and they occasionally actually succeeded—a diet of 5,000-7,000 calories per day with frequently disastrous effects upon the gastrointestinal tract. In 1908, Fisher reported that ninety-five sanatoria located in various parts of the world served a diet of 2,140 to 5,500 calories per day with a protein content of from 60 to 190 grams. Recently, due to a better understanding of the pathology of tuberculosis, the over-feeding of patients has ceased in our larger sanatoria but there are still many physicians who believe that tuberculosis is cured by a high protein diet.

If we couple the economic background of an inadequate food supply with the medical background which is based on the picture of tuberculosis as

it is characterized by the word "consumption", we at once see the reason for the importance of diet in the treatment of tuberculosis

In 1919, McCann applied the modern methods of study of nutritional requirements of man to the dietetic requirements of the tuberculous. As a result of these studies he estimated that the daily energy requirements of the consumptive at absolute bed rest ranged from 1760 to 2640 calories per day. The estimation was founded upon the basal heat production plus additions to the diet in accordance with the amount of fever present. He also called attention to the apparent antagonistic metabolic factors in a disease causing abnormal wasting which should be corrected by a high caloric diet but whose cure lies in pulmonary rest. While such a diet might counteract the wasting, yet the resulting accelerated metabolic rate would increase the pulmonary activity. This is contrary to the aim of the present day treatment. Mayer and Kugelmass estimated that the diet which they consider as ideal for the tuberculous individual would accelerate metabolism thirty-seven per cent and hence interfere with the desired pulmonary rest. McCann and Bari in 1920 concluded that as "the food requirements of tuberculous patients are not large either as regards total energy value or nitrogen content, forced feeding is unnecessary and is probably harmful in the active stages of pulmonary disease. Since protein increases the respiratory exchange in the tuberculous as well as the normals it may be well to limit the protein intake during periods of activity in order to put the lungs at

rest." Therefore, it seems that the ideal diet for the consumptive is one which will enable the individual to maintain normal nutrition and his sense of well-being with a minimum amount of pulmonary activity. McCann believes that this can best be obtained by a diet consisting of sixty to ninety grams of protein with fat up to the limit of digestive capacity and a sufficient amount of carbohydrates to raise the caloric value of the diet to 2500 to 3000 calories per day.

While tuberculosis is distinctly an infectious disease, often accompanied by gastrointestinal and nutritional disturbances, rather than a nutritional one man is still searching for a diet which will improve the patient's chance for recovery. Recently Sauerbruch, Gerson and Herimannsdorfer announced such a diet. This represents an attempt on the part of Herimannsdorfer to adapt a diet, previously used with excellent results by Dr. Gerson in the healing of wounds, to the treatment of lupus and later of pulmonary and bone and joint tuberculosis. He aimed to correct the excessive tissue hydration which occurs in tuberculosis by so planning the diet that the sodium chloride content of the urine is reduced to 0.2 to 0.3 grams per day. This is to be done through the substitution of mineralogen, a mixture of inorganic compounds containing 70 per cent of calcium phosphate and lactate for table salt. While mineralogen contains a preponderance of alkali-forming salts the German clinicians claim that its chief value lies in its acid-forming properties. Its chemical composition together with the fact that a number of its con-

stituents are absorbed so slightly in the alimentary canal that they can have very little if any effect upon the acid-base equilibrium, makes this contention very doubtful

The diet permits fifty calories per kilogram weight per day with an average maximum of 3500 calories in the ratio of protein 15, fat 17 and carbohydrate 37. This gives a protein allowance of 92 grams per day which the Europeans consider low but which we do not, as the diet in the average American sanatorium consists of 70 to 100 grams of protein. The fat content of this diet is relatively high and the carbohydrate content relatively low because carbohydrates reduce resistance to infection in general. The chief sources of protein are milk and eggs and milled products, as only 500 grams of fresh meat are permitted weekly.

One of the outstanding features of this diet is a relatively large amount of vitamins from A to G inclusive. Fruits and vegetables, either fresh or cooked, which are abundant in vitamins, are used freely as is phosphorated cod liver oil, a teaspoonful of which is given with each meal. The list of restricted and permitted foods is long and has been given elsewhere, so it will be omitted from this discussion. Every attempt, however, is made to improve the palatability of the food and to compensate for the lack of its salt. In Munich the results of this diet have apparently been extremely beneficial in lupus but not so beneficial in bone and joint tuberculosis and its value in the treatment of pulmonary tuberculosis has not been so easily determined.

Mayer and Kugelmass' report on twenty patients at Saranac Lake who failed to gain on the accepted therapy over a period of two or three years previous to the use of this diet is very interesting. On this diet the symptoms improved, there was partial x-ray clearing in about a third of the cases but the sputum remained positive in all cases. Two very stubborn cases of intestinal tuberculosis cleared up clinically and x-ray filling defects of the colon disappeared. The results obtained were in general accord with those obtained in similar studies made on rats maintained on an acid forming and base forming diet respectively. Clarence Emerson, of the Lincoln General Hospital, reports favorably on a series of ten patients treated with this diet over a period of twelve months. While he is apparently not unduly enthusiastic about it, still he believes that this diet favors an improvement in tuberculosis. Martin, on the other hand, believes that one should strive for a slight alkalosis of the blood and tissues rather than for an acidosis, while Von Baeyer reports that his tuberculous patients thrive on a dry diet.

Myers stresses vitamin A particularly, while McConkey and Smith believe that all vitamins are of extreme importance in tuberculosis and other chronic infections. McConkey reports that the healing of intestinal ulcers is markedly improved through the administration of cod liver oil and tomato juice, rich sources of vitamins A, B, C and D. He also claims that the oral administration of 25 grams of irradiated cholesterol, 1 gram of concentrated cod liver oil and 10 grams

of irradiated yeast daily is just as effective in the treatment of intestinal tuberculosis as is artificial heliotherapy. He adds, however, that irradiated cholesterol is apparently less effective than the others as it was fed to nine children with bone and joint tuberculosis for four months without any appreciable effect upon the healing process or increase in blood calcium or phosphorus. His report calls attention to the fact that apparently there is close relationship between the beneficial effects of heliotherapy and the increased formation of vitamin D as a result of the solar radiation.

The research work on the effect of diet in experimental tuberculosis seems to center about the use of calcium and the vitamins. Because calcium is so frequently found in healed lesions of tuberculosis, numerous attempts have been made to influence the rapidity of the healing process by increasing the blood calcium. That naturally raises the question as to whether there is a diminution in blood calcium in tuberculosis. According to Greisheimer and Van Winkle, tuberculosis is not characterized by a demineralization although the "C" group of cases showed lower calcium value than any of the other groups. Gordon and Cantarow claim that an increase in the normal calcium content of the blood has apparently no influence on the tuberculous process. McRae and Ingvaldson claim that "as vitamin D causes calcification in rickets, we may conclude that it should do likewise in tuberculosis." Grant, Bowen and Stegeman conclude that when calcium and vitamin D are decreased sufficiently there is a definite lowering of

the resistance to tuberculosis in rats and conversely that rats maintained on adequate diets could withstand many times the dose of tubercle bacilli which produced tuberculosis in rats maintained on a deficiency diet. Because of this they believed that the vitamin D content of the diet should be increased in gloomy weather to compensate for the lack of sunshine. An analysis of Grant's report in 1930 warrants one in concluding that she believes that when a diet is deficient the addition of vitamin D does not retard the tuberculous process but if the diet is already adequate a further addition of vitamin D seems to increase the resistance to tuberculosis, though a prolonged excess of vitamin D seems to lower it. She called attention to the fact that resistance to tuberculosis can be reduced by a prolonged disturbance in the optimal balance which should exist between calcium and vitamins C and D of the diet *without destroying the growth impulse*. McConkey and Smith claim that a diet partially deficient in vitamins A, C and D renders guinea pigs susceptible to intestinal tuberculosis. They believe that "a chronic partial deficiency of vitamin C is the most important factor in the production of clinical disease."

As the importance of vitamins in the diet is generally accepted the question of the value of commercial preparations of vitamins is raised. In this connection McCollum writes: "The fact that we can readily prepare diets from ordinary foods which will contain several times the minimum amount of vitamins upon which apparently normal nutrition can be maintained over a considerable period of

time, tends to render academic the discussion about the advisability of taking concentrated commercial preparations of vitamins."

Hawes' report of the answers of thirty-six physicians to the following eight questions is very interesting as it indicates modern practice

1 Do you believe in lunches between meals? If so, under what conditions? Lunches between meals are rarely advisable. The average patient enjoys his food more and takes larger amounts of nourishment when he confines himself to three meals a day than in any other way

2 Do you advise egg-nogs? Egg-nogs in any form at any time are as Dr. Carroll Edson says, "An invention of the devil"

3 Do you believe in raw eggs? If so, how do you advise the patient to take them? Raw eggs are easily borne and if the patient is under weight, do not do any harm and may do good. They are not so digestible as cooked eggs and on the whole are rarely indicated

4. As a general proposition, how much extra milk is advisable? About one quart of milk a day, four or five glasses with meals, is the maximum amount that should be given. A glass of milk with each meal is usually sufficient

5 Do you lay down any definite laws about what special foods should be emphasized? There are no special foods that need be emphasized. Fruits and vegetables will help correct constipation. They contain vitamins but little if any nourishment. Potatoes, macaroni and rice contain much food value

6. Do you give any special directions about the care of the bowels? The bowels should act at least once daily. A mild laxative once a week is often a valuable help if a diet with plenty of roughage is not enough

7 Do you advise using large quantities of water? Five or six glasses of water with and between meals is advisable in every case

8 Do you emphasize rest before and after each meal? A rest before and especially after each meal is essential. The dictum approach and leave each meal in a rested condition is an especially good one to adhere to

Modern man has so developed his food supply that the poor man of today has a more varied and stable diet than did the wealthy man of a few centuries ago. For instance, due to the improvements in the canning industry we now have vegetables the year around. Therefore we no longer feel as run down in the spring as did our ancestors who took sulphur and molasses as a spring tonic

But even with his wonderful opportunities for a stable and well-balanced diet, modern man, particularly in Europe and America, is, in the opinion of McCollum, deriving too large a proportion of his food from cereals (35 to 45 per cent) supplemented by muscle meats, potatoes and sugar. He states that this combination of food does not support satisfactory development, longevity and fertility in any of the animals with which experimental studies have been conducted. Cereals which form the bulk of the diet are comparatively cheap but when used singly are deficient in proteins. When used in various combinations the pro-

tein deficiency of one individual cereal is supplemented by the protein content of another. Muscle meats are similar to cereals in that they are deficient in calcium and sodium chloride but they have become very palatable and modern man is using them freely to the exclusion of the rest of the carcass, thereby losing the protective foods which it contains. If man used more of the carcass as does the carnivorous animal, his diet would be better balanced and would not need to be supplemented by the protective foods. Carbohydrates, with the exception of honey which contains a small amount of vitamin B, are lacking in vitamins and their excessive use lowers the resistance of the body to infection in general.

Because of the deficiency of the above diet, it is necessary to supplement it by certain protective foods in order to improve nutrition and skeletal development and to increase the resistance of the body to infection in general. Milk, eggs, leafy vegetables and fruits belong to this group of foods. Milk is a very satisfactory article of food but it is inadequate when used as a sole source of nourishment over a long period of time. When used in combination with other foods it supplies their deficiency. Eggs are also very valuable for increasing the palatability of other foods, and are rich in vitamins A and D but poor in vitamin B. They are also deficient in calcium and favor putrefactive processes in the gastrointestinal tract but this tendency is counteracted when combined with carbohydrates and milk. Sea foods are very satisfactory sup-

plementary foods because the entire edible portion of the animal is used.

McCollum calls attention to the fact that there are two general types of deficiency diets, one which is marked and is followed by an acute reaction as beri beri or scurvy and a slight borderline deficiency which must be continued over a long period of time before its effect is felt. It is this latter type of deficiency diet which, because of its insidious nature, is so pernicious and harmful for man. There is much evidence to show that a good state of nutrition increases greatly the resistance of the body against certain types of infection while, on the other hand, an improper diet will cause inferior physical development, lack of recuperative powers and endurance and may result in accumulative fatigue with a lack of resistance to those infectious diseases where specific immunity is not usually developed.

That the skeletal development of man can be markedly influenced by diet is evidenced by the fact that the Japanese children born in this country and fed on an American diet will in the second and third generation be considerably larger than children of the same age who lived on a Japanese diet. Grant's conclusions also call attention to the fact that there is of necessity no specific relationship between the skeletal development or size and weight and resistance to tuberculosis. Russell reports as the result of his clinical observation on a number of dispensary cases, that while nutrition may have a marked effect upon the symptoms of tuberculosis it failed specifically to effect the course of the disease. That recalls a statement of Stewart

time, tends to render academic the discussion about the advisability of taking concentrated commercial preparations of vitamins "

Hawes' report of the answers of thirty-six physicians to the following eight questions is very interesting as it indicates modern practice

1. Do you believe in lunches between meals? If so, under what conditions? Lunches between meals are rarely advisable. The average patient enjoys his food more and takes larger amounts of nourishment when he confines himself to three meals a day than in any other way

2. Do you advise egg-nogs? Egg-nogs in any form at any time are as Dr. Carroll Edson says, "An invention of the devil "

3. Do you believe in raw eggs? If so, how do you advise the patient to take them? Raw eggs are easily borne and if the patient is under weight, do not do any harm and may do good. They are not so digestible as cooked eggs and on the whole are rarely indicated

4. As a general proposition, how much extra milk is advisable? About one quart of milk a day, four or five glasses with meals, is the maximum amount that should be given. A glass of milk with each meal is usually sufficient

5. Do you lay down any definite laws about what special foods should be emphasized? There are no special foods that need be emphasized. Fruits and vegetables will help correct constipation. They contain vitamins but little if any nourishment. Potatoes, macaroni and rice contain much food value

6. Do you give any special directions about the care of the bowels? The bowels should act at least once daily. A mild laxative once a week is often a valuable help if a diet with plenty of roughage is not enough

7. Do you advise using large quantities of water? Five or six glasses of water with and between meals is advisable in every case

8. Do you emphasize rest before and after each meal? A rest before and especially after each meal is essential. The dictum approach and leave each meal in a rested condition is an especially good one to adhere to

Modern man has so developed his food supply that the poor man of today has a more varied and stable diet than did the wealthy man of a few centuries ago. For instance, due to the improvements in the canning industry we now have vegetables the year around. Therefore we no longer feel as run down in the spring as did our ancestors who took sulphur and molasses as a spring tonic

But even with his wonderful opportunities for a stable and well-balanced diet, modern man, particularly in Europe and America, is, in the opinion of McCollum, deriving too large a proportion of his food from cereals (35 to 45 per cent) supplemented by muscle meats, potatoes and sugar. He states that this combination of food does not support satisfactory development, longevity and fertility in any of the animals with which experimental studies have been conducted. Cereals which form the bulk of the diet are comparatively cheap but when used singly are deficient in proteins. When used in various combinations the pro-

tein deficiency of one individual cereal is supplemented by the protein content of another. Muscle meats are similar to cereals in that they are deficient in calcium and sodium chloride but they have become very palatable and modern man is using them freely to the exclusion of the rest of the carcass, thereby losing the protective foods which it contains. If man used more of the carcass as does the carnivorous animal, his diet would be better balanced and would not need to be supplemented by the protective foods. Carbohydrates, with the exception of honey which contains a small amount of vitamin B, are lacking in vitamins and their excessive use lowers the resistance of the body to infection in general.

Because of the deficiency of the above diet, it is necessary to supplement it by certain protective foods in order to improve nutrition and skeletal development and to increase the resistance of the body to infection in general. Milk, eggs, leafy vegetables and fruits belong to this group of foods. Milk is a very satisfactory article of food but it is inadequate when used as a sole source of nourishment over a long period of time. When used in combination with other foods it supplies their deficiency. Eggs are also very valuable for increasing the palatability of other foods, and are rich in vitamins A and D but poor in vitamin B. They are also deficient in calcium and favor putrefactive processes in the gastrointestinal tract but this tendency is counteracted when combined with carbohydrates and milk. Sea foods are very satisfactory sup-

plementary foods because the entire edible portion of the animal is used.

McCollum calls attention to the fact that there are two general types of deficiency diets, one which is marked and is followed by an acute reaction as seen in beriberi or scurvy and a slight borderline deficiency which must be continued over a long period of time before its effect is felt. It is this latter type of deficiency diet which, because of its insidious nature, is so pernicious and harmful for man. There is much evidence to show that a good state of nutrition increases greatly the resistance of the body against certain types of infection while, on the other hand, an improper diet will cause inferior physical development, lack of recuperative powers and endurance and may result in accumulative fatigue with a lack of resistance to those infectious diseases where specific immunity is not usually developed.

That the skeletal development of man can be markedly influenced by diet is evidenced by the fact that the Japanese children born in this country and fed on an American diet will in the second and third generation be considerably larger than children of the same age who lived on a Japanese diet. Giant's conclusions also call attention to the fact that there is of necessity no specific relationship between the skeletal development or size and weight and resistance to tuberculosis. Russell reports as the result of his clinical observation on a number of dispensary cases, that while nutrition may have a marked effect upon the symptoms of tuberculosis, it failed specifically to effect the course of the disease. That recalls a statement of Stewart

"that we put patients to bed because of symptoms and a lesion. We are prone to forget about the lesion and let them up when the symptoms have disappeared." Loss of weight is one of the symptoms of tuberculosis and we are all too apt today to forget about the lesion when the symptoms have disappeared and man's nutrition is back to normal or a little above and to conclude, as did the ancients that the individual is well.

CONCLUSIONS

There is much evidence to prove that there are certain minimum requirements as far as proteins, fats, carbohydrates, vitamins and minerals are concerned in order that normal health may be maintained. Metabolic studies in tuberculosis prove that increasing the diet beyond a certain point is detrimental to the cure of pulmonary tuberculosis because of the increased pulmonary activities necessitated by the increase in metabolism. As we believe that a diet which is well balanced and adequate for a man in health is sufficient as the basic diet for the person with tuberculosis, Glen Lake Sanatorium has prepared such a diet which, unless there is definite gastrointestinal pathology, or nutritional disturbances present, is essentially the same as would be provided for the non-tuberculous individual who is living under the same relative conditions of exercise. When however, such conditions are present, they should, of course receive just as prompt and careful treatment as they would, should they occur in a person without tuberculosis. The diet as planned provides

for about 3000 calories per day and includes half a pint of milk with each meal and at bed time, and contains 70 to 100 grams of protein and about 300 grams of carbohydrates. The balance is composed of fat. Those who are below weight receive an extra half pint of milk in the morning and afternoon. Of course, this is merely the basic diet and is modified as occasion demands. Out of a population of 640 adults we have at times served as high as a 125 special diets.

In planning this diet we have followed the general suggestions of McCollum as to the most satisfactory type of diet which represents "the best elements from those several systems of diets which have been thoroughly tested in human experience and have been found successful." In brief, these are, that if the protective foods such as dairy products, including one quart of milk daily and leafy vegetables, are used freely and also a certain amount of raw vegetables and fruits for their antiscorbutic properties (we use a fairly large amount of canned vegetables also which if one can judge from Byrd's two years' experience at the South Pole are also antiscorbutic) "the remainder of the food supply may safely be derived from any of our ordinary milled cereal products, tubers, root vegetables, sugar, and meats. Infants and children can be safeguarded in their skeletal development by providing at regular intervals a suitable amount of cod liver oil, and by affording an opportunity for outside exercise in sunlight."

REFERENCES

- BAAS, I H History of medicine, translated by H F Henderson, 1889, J H Bask and Company
- CLARK JAMES Treatise on pulmonary consumption 1835, Carey, Lea and Blanchard, Philadelphia
- EMERSON, C Treatment of tuberculosis by altering metabolism through dietary management (Gerson-Sauerbruch Method), Nebraska State Med Jr 1920, xiv, 104
- FISHER, IRVING Proc Sixth Internat Cong on Tuberculosis, 1908, Part 2 1691, and is reported by McCann and Barr, Arch Int Med, 1920, xxi, 663
- FLICK Development of our knowledge of tuberculosis, 1925, Wickersham Printing Co, Philadelphia
- GORDON and CANTAROW Effect of parathyroid extract and calcium upon calcification and healing in pulmonary tuberculosis, Am Rev Tuberc, 1920, x, 901-907
- GRANT, AGNES H The effect of rachitic diets on experimental tuberculosis, resistance to tuberculosis decreased by adding cod liver oil, Am Rev Tuberc, 1930, xxi, 102
- GRANT, AGNES H The effect of rachitic diets on experimental tuberculosis, effects of disturbing optimal ratio between calcium, vitamin C and vitamin D, Am Rev Tuberc, 1930, xxi, 115
- GRANT, BOWEN, and STEGEMAN The effect of rachitic diets on experimental tuberculosis in white rats II Vitamin D deficiency as a factor in lowering resistance, Am Rev Tuberc, 1927, xvi, 642
- GRANT, SUFENAGA, and STEGEMAN The effect of rachitic diets on experimental tuberculosis in white rats I Calcium and Vitamin D deficiencies as factors in lowering resistance Am Rev Tuberc, 1927, xvi, 628
- GREISHELMER and VAN WINKLE Plasma calcium in tuberculous adults, Am Rev Tuberc, 1926, xv, 270
- HAWES, J Diet in tuberculosis, Jr Am Med Assoc, 1929, xciii, 452
- HIPPOCRATES Genuine works of Hippocrates, volume I, translated by Francis Adams, Sydenham Society, London, 1849, Ancient Medicine
- KRAMER, B, GRAYZEL, H G, and SHEAR, M J Vitamin D in tuberculosis, Proc Soc for Exp Biol and Med, 1929, xxxii, 144
- MARTIN, E S Food problem in a sanatorium, Am Rev Tuberc, 1928, xvii, 557
- MARTIN, C Zur Frage der diätetischen Behandlung der Lungentuberkulose, Ztschr f Tuberk, 1926, xli, 132-136
- MAYER, E, and KUGELMASS, N Basic (vitamin) feeding in tuberculosis, Jr Am Med Assoc, 1929, xciii, 1856
- MCCANN, W S The dietary requirements in pulmonary tuberculosis, Am Rev Tuberc, 1922, v, 870
- MCCANN, W S, and BARR, D P Clinical calorimetry The metabolism in tuberculosis, Arch Int Med, 1920, xxvi, 663
- MCCOLLUM and SIMMONDS Newer knowledge of nutrition, 4th Edition, 1929, Macmillan Co, New York
- MCCONKEY, M The treatment of intestinal tuberculosis with cod liver oil and tomato juice, Am Rev Tuberc, 1930, xxi, 627
- MCCRACK and INGVALDSON Lipoid phosphorus cholesterol ratio before and after feeding radiated eggs to tuberculous patients, Am Rev Tuberc, 1928, xvii, 520
- MYERS, J A Diet in the treatment and prevention of tuberculosis, Minn Med, 1926, ix, 121-124
- RUSSELL, J F Length of treatment and mortality in arrested cases of pulmonary tuberculosis, a resume of the after histories of 121 cases and a proposed plan to lengthen the period of treatment, Am Rev Tuberc, 1927, xvi, 145-156
- SAUERBRUCH, F, HERRMANNSDORFER, A, and GERSON, M Über Versuche, schwere Formen der Tuberkulose durch diätetische Behandlung zu beeinflussen Über Tuberkulosebehandlung durch diätetische Umstellung im Mineralbestande des Körpers von A Herr-

- mannsdorfer, Munch med Wchnschr, 1926, lxxiii, 47
- SAUERBRUCH, F, and HERRMANNSDORFER, A Ergebnisse und Wert einer diatetischen Behandlung der Tuberkulose, Munch med Wchnsch, 1928, lxxv, 35
- SHIRCLIFFE, ARNOLD Edgewater Beach Salad Book, Chicago Hotel Monthly Press, 1926
- SMITH, DAVID T and McCONKEY, M Experimental intestinal tuberculosis in the guinea pig, induced by feeding tubercle bacilli to animals living on a diet deficient in vitamins, Trans Nat Tubercul Assoc, 1929 Twenty-fifth annual meeting
- VON BAER, H Trockenkost zur Behandlung von Knochentuberkulose Zentralbl f Chir, 1927, liv, 3080-3081
- WILLIAMS Pulmonary consumption, 1887, Longmann, Green and Company, London

Editorials

BLOOD CHANGES IN BENZOL POISONING

In the nine years since Schultz described the condition now known as agranulocytic angina, it has become a disease of frequent occurrence. It is now evident that it is not an entity as was first believed, but rather a group of conditions, for in some cases there is granulocytopenia without angina, in others a severe aplastic anemia, and in still others a hemorrhagic diathesis dominates the clinical picture. Likewise there is a wide range of conditions with which granular leukopenia may be found associated: radium and X-ray irradiation, administration of arsenic compounds and especially asphenamine, benzol and its homologues and substitution products, and with pernicious anemia, aleukemic lymphoblastoma and lymphatic and myelogenous leukemia. With these there may or may not be sore mouth and angina. A necrotizing process against which the defensive powers of the body are powerless, or nearly so, may seem to have its origin in an operative wound, or to arise *de novo* on parts well away from the mouth. Does this group of morbid conditions constitute a new disease-concept or have we always had it with us? Is the apparent wave of leucopenic, aplastic anemic, and myelophthisic conditions, variously styled, the result of directed attention and therefore of better diagnosis? It so happens that certain of the known agencies capable of producing similar

effects upon the bone marrow and blood are those whose industrial and therapeutic use is rapidly increasing. What part of the increase may be thus explained no one can as yet determine.

The effect of benzol upon the blood and blood forming organs has been studied from the standpoint especially of the important industrial hazard which exists. Benzol (*benzene*, not *benzine*) is used for its solvent action, its fuel value, and as a starting point in the manufacture of various synthetic drugs, dyes and other products. It is employed in a variety of industries, including many branches of the manufacture of rubber, artificial leather and leather enamels, waterproof fabrics including rubber raincoats, window shades, lacquers, shellacs, paint removers, bronzing liquids and batteries, in dry cleaning, and in many other ways. For the past six years the annual production of benzol in this country has not fallen below 100,000,000 gallons.

In the present year two very important studies of benzol poisoning have appeared: a comprehensive review by Alice Hamilton* and an analysis of the literature with much original material added, by Carey P. McCord**.

*ALICE HAMILTON, M.D., Benzene (benzol) poisoning, *Arch. of Path.*, 1931, xi, 434-454, 601-637.

**CAREY P. MCCORD, M.D., Benzol (benzene) poisoning, a new investigation of the toxicity of benzene and benzene impurities, 1931, from The Industrial Health Conservancy Laboratories, Cincinnati, Ohio.

Their conclusions in regard to the blood are especially important. In the early stage of benzol action a leucopenia is not found, but on the contrary, the white cells are usually moderately increased. Continued exposure leads to a significant leucopenia, oftentimes as low as 500 cells per cubic millimeter if exposure is continued. Very rarely a leucocytosis persists. The establishment of an arbitrary level of depression of the white count as indicative of benzol poisoning has certain inherent dangers. The normal variation of an individual may swing over a range in which the maximum is 100 per cent greater than the minimum. Thus a fixed standard, such as that a decrease of 25 per cent from the normal white blood cell count constitutes a fair index of the presence of benzol poisoning, providing other conditions can be ruled out, must be applied with caution. Nevertheless, in the presence of this industrial hazard a sustained leucopenia of 25 per cent or more as based upon a knowledge of normal counts of the individual, is of diagnostic value, and any white blood cell count in the neighborhood of 5,000 or less in a benzol worker is fair evidence of poisoning if this degree of leucopenia persists in several counts distributed over one or more days. The red cells suffer a less severe reduction than the white cells. In the late stage of cases destined to be fatal red blood cell counts as low as 1,000,000 or even 500,000 have been found. Under the influence of benzol, basophilic red cells are present in numbers far higher than normal and occasional nucleated red cells are seen, but poikilocytosis, anisocytosis and hemolysis are by no means

constant, and in respect to these the literature is conflicting. The hemoglobin falls in proportion to the diminution in red blood cells, for the anemia is dependent upon injury to the bone marrow and not upon hemolysis. McCord was unable to find significant points of differentiation between the blood picture of benzol poisoning and that of the agranulocytosis of Schultz's angina. In all but the early stage of benzol poisoning the platelets are decreased and bleeding time is frequently prolonged. With platelet counts below 30,000, spontaneous hemorrhages are said to appear. Finally, and of great significance in duplicating the picture of agranulocytic angina, it has been shown by numerous workers that benzol may lower the infection-resisting powers of the body by diminishing antibodies. In fatal cases of chronic poisoning with benzol, infection nearly always plays a part and not infrequently necrotizing infectious lesions of the mouth are present. Thus in seeking extrinsic factors in the etiology of the leukopenic diseases benzol and its allies must be kept constantly in mind.

SAFETY FIRST

Seldom, indeed, has the physician been found deaf to a legitimate call for his services, a shirker when confronted with duty, or a coward. Neither has his apparent disregard for personal comfort and security been based upon ignorance of possible consequences to himself. At the present time it must be exceedingly rare for an emergency to arise in which a physician finds it necessary to aspirate a diphtheritic membrane from the

larynx of a dying child by mouth to mouth contact. It was not the discovery of the Klebs-Loeffler bacillus, however, which caused this act of heroism to become all but unknown at the present time. That the physician is responsive to duty without regard to himself is generally known, and the resulting situation has become part of the stock in trade of the outlaw. According to press reports, a Fellow* of the American College of Physicians received an emergency call over the telephone requesting him to go to a certain address, with the added appeal, "Please come quick, doctor, the baby is dying of pneumonia." Experiencing some difficulty in finding the number given, he was lured into a dark, and as afterwards appeared, vacant house by a man in the doorway who said, "Please hurry, doctor." Within the house he was struck repeatedly with a black jack, robbed of money and wrist watch and left dazed and apparently unconscious. After an interval he was able to recover his keys from the floor, reach his car, drive home, and summon aid. Such incidents have become increasingly more frequent. Robbery always has been the motive with sometimes assault added, as in the example recounted, or kidnapping. In the face of another year of economic stress, it cannot be hoped that the danger will be lessened. In some cities this situation has been met by arrangements with the police departments such that a physician answering night calls can, if he desires, have escort, or be met at the stated address by a police officer. This is easily man-

aged where radio-controlled scout cars are used for night patrol. The physician telephones his destination and time of arrival and his escort meets him at the address given or at a nearby street intersection. Through existing organizations physicians can properly request such aid in the performance of their recognized duty. Where similar plans are already in operation, physicians should not hesitate to avail themselves of the protection offered.

THE STANDARDIZATION OF AMERICAN SPECIALISTS

Several articles have appeared in the medical press of America during recent years concerning what might be termed the standardization of specialists. Under present conditions anybody who chooses to, provided he is qualified and registered, can set up office as a specialist in any of the many branches of medicine. He may or may not have any particular knowledge of the subject he professes to specialize in. I think, however, the great majority of men make it their business to take special instruction over a period of six to twelve months in the subject or subjects they wish to specialize in. The public as a whole expects great things of the specialist, and certainly takes it for granted that he possesses infinitely superior knowledge of his subject than his unfortunate much-maligned brother, the general practitioner, the public occasionally is quite wrong in this supposition. It would certainly appear that a more or less fixed standard is necessary, and as far as medicine is concerned I am of opinion that the American College of Physicians can be of tremendous

*M. K. Wylder, B.S., M.D., F.A.C.P., Albuquerque, N. M.

assistance in dealing with this problem. It should be a sort of "*sine qua non*" that no physician could be accepted as having joined the ranks of specialism proper unless he possessed at minimum the Associateship of the American College of Physicians. In some way or other the general public should be thoroughly instructed and made to understand this. It would be well if the Board of Regents and the Committee on Credentials at an early date very carefully considered the important and pressing question of holding an examination proper either written or clinical or both for admission to Associateship in the College; this might be held after the ordinary pre-

liminaries of investigation of the candidate's worth and suitability for nomination have been gone into in the usual way by the Executive Secretary and Committee on Credentials. This, to my mind, is the only practical way of facing the problem, and the examination of the American College of Physicians will have to be looked up to and known throughout the country as the hall-mark of specialization of the American continent, so far as medicine is concerned.

(Contributed Editorial by G A PEMBERTON WRIGHT, F A C P , M C P and S (Ont), L A H (Dub), Ph C (Irel), Kingston, Jamaica)

Abstracts

Der Abbau des Blutfarbstoffes im Verdauungstrakt des gesunden Menschen
(*The Breaking Down of Blood Pigment in the Digestive Tract of Healthy Men*)
By FELIX HAUROWITZ (Arch f Verdauungs-Krankh, 1931, 1, 33-46)

After the ingestion of 50 cc of the subject's own blood, the feces were subjected to chemical analysis in order to determine the amounts of the various derivatives of blood pigment present. Control analyses were made for several days before ingesting the blood and the subject was maintained on a blood- and chlorophyll-free diet. By far the greater part of the blood pigment was recovered on the second and third days following ingestion as protohematin. Three groups of analyses showed an output of 85 to 90 per cent as protohematin, 5 to 8 per cent as deuterohematin, 2 to 3 per cent in the protoporphyrin fraction and $\frac{1}{2}$ to 1 per cent in the deuteroporphyrin fraction. The excretion of coproporphyrin was not significantly influenced by the ingestion of blood. Deuterohematin, and proto- and deuteroporphyrin are not derived from blood pigment through the agency of enzymes but through putrefaction. Native blood pigment (oxyhemoglobin and reduced hemoglobin) was not found in the stools. This is in agreement with the known rapid alteration of native blood pigment produced by gastric acidity. On the other hand alkaline trypsin solution alters blood pigment so slowly that native blood pigment may be demonstrated even after 24 hours. Thus the demonstration of occult native blood pigment (by its characteristic spectrum) in the feces comes to be of diagnostic significance in differentiating between bleeding into the acid stomach contents, or into an achylic stomach or the alkaline upper small intestine, providing a source of blood from a lower level can be excluded. Methods for the analysis of feces for the qualitative and

quantitative recognition of the various blood pigment fractions are given in detail.

The Elimination of Phenolsulphonphthalein by the Kidney. The Influence of Pathologic Changes in the Liver. By J P HANNER, M D, and G H WHIPPLE, M D, Rochester, N Y (Arch Int Med, 1931, xlviii, 598-610)

For many years it has been known that an unusually high degree of renal elimination of phenolsulphonphthalein occurs in certain cases of toxemia or pregnancy. It was suspected that these cases were complicated by some abnormality of the liver. This question has been investigated by carefully controlled experiments in which liver injury has been produced in dogs by various means, and also by the determination of the mode of excretion in animals with complete obstruction of the common bile duct. It was found that the normal dog excretes from about 10 to 15 per cent of the usual dose of phenolsulphonphthalein by the hepatic route. When this pathway is blocked, the surplus appears in the urine, giving figures proportionately higher than would otherwise be found. Of that portion which escapes into the intestines in the normal animal, not more than 5 per cent is absorbed, so that reabsorption of the dye from the bile can be dismissed as a factor of no importance. In dogs with necrosis of the liver due to chloroform poisoning there is a distinct rise in the elimination of phenolsulphonphthalein by the normal kidney. With repair of the hepatic injury, the elimination of phthalein returns to normal. Phosphorus gives a similar but less striking reaction. After hepatic injury due to chloroform, the dog's liver does not remove phenolsulphonphthalein from the blood stream and does not excrete it in the bile. The portion which otherwise would have been removed by this route is therefore available

for excretion by the kidneys. Clinically, therefore, an unusually high renal elimination of phenolsulphonphthalein should suggest pathologic changes in the liver, and in the presence of combined renal and hepatic disease, great caution should be exercised in the estimation of the amount of renal injury.

A Study of the Blood Picture in Congenital Syphilis and the Effect of Antisyphilitic Therapy upon the Hemoglobin and Cellular Elements By H. HARRIS PERLMAN, M.D., and CARROLL S. WRIGHT, M.D. (Am. Jr. Syph., 1931, xv, 449-495)

Thirty-four patients with congenital syphilis were selected for this study. Diagnosis of syphilis was based upon history of the disease as existing in either parent, with clinical or roentgenographic manifestations and positive serologic reactions in the child. In age, these patients ranged between 2 and 14 years. Twenty-seven normal children within the same age range were used as a comparative normal control, and as a further control a group of 22 non-syphilitic, but under-nourished, children was established. It was found that the secondary anemia present in congenital syphilis does not differ from the anemias associated with various chronic infections, and that in both degree and kind, it may not differ from anemias which are discoverable in supposedly healthy children. No reliance could be placed upon the degree of anemia as a diagnostic sign, nor did the study of the individual cell types of the blood reveal anything of diagnostic or prognostic importance. Blood studies were carried out before and after various forms of antisyphilitic therapy. Arsenic or bismuth or a combination of these drugs was found to have a variable and inconsistent effect upon the secondary anemia and upon the differential count. In certain groups there was a greater loss than gain in hemoglobin, but in no single series was there any striking change referable to the treatment used.

A Study of Nephritis at the Canton Hospital By WILLIAM W. CADBURY, A.M., M.D., F.A.C.P. (Transactions of the Eighth Congress of the Far Eastern As-

sociation of Tropical Medicine, Bangkok, December, 1930. 19 pages.)

There is very little to be found in medical literature concerning nephritis among native Chinese. The general impression that Bright's disease is less prevalent in China than in Europe and America seems to be borne out by such statistics as could be collected, but the difference is not very great. In twenty-three institutions in China it was found that the percentage of nephritis to all hospital admissions varied from 0.25 to 1.00 in ten, from 1.02 to 1.69 in eleven, and in only two did the ratio exceed 2.00 per cent. In five large hospitals in the eastern part of the United States relative incidence of nephritis to all cases admitted varied from 1.33 to 3.18 per cent. The percentage of nephritis cases to medical admissions only was between 2 and 3 in four Chinese Hospitals, between 3 and 4 in five, 4.04 at Canton Hospital, 4.09 at Peiping Union Medical College, and over 6.00 at Hackett Hospital in Canton and the Government Civil Hospital in Hong-kong. In the five hospitals of the United States, with which comparison is made, the incidence of nephritis to medical admissions varied from 3.63 to 7.61 per cent. A larger proportion of nephritis cases was found in the hospitals of south and central China than in those of north China.

The Effect of Cortin in Asthenia By FRANK A. HARTMAN and GEORGE W. THORN (Proc. Soc. for Exp. Biol. and Med., 1931, xxix, 48-50)

The effect of cortin in the asthenia of a number of clinical conditions including Addison's disease has been investigated. Since increased susceptibility to fatigue is more significant in such conditions than the actual dynamic power of the muscle, a finger ergometer was used to test the threshold of fatigue. Four normal individuals showed a maximum increase in power to do work before the development of fatigue of from 50 to 500 per cent. The effect of cortin on the fatigue point was studied in six cases of Addison's disease, two in which the cortical insufficiency was almost absolute and four in which it was less marked. The threshold of fatigue was advanced 700 per

cent in one of the severe cases and none in the other. One of the less severe cases showed no increase, two increased 400 per cent and the fourth, 4900 per cent. Other conditions associated with asthma, in which improvement in susceptibility to fatigue, either symptomatic or ergometric or both, followed administration of cortin, were pregnancy, Graves' disease, muscular dystrophy, osteomyelitis, diphtheria and myasthenia gravis.

Cerebral Adiposity with Mental Deficiency and Retinitis Pigmentosa. The Lawrence-Biedl Syndrome. By EDWARD WEISS, M.D. (Endocrinology, 1931, xv, 435-441.) Lawrence and Moon in 1866, Bardet in 1920, and Biedl in 1922, described a familial condition in which the affected individuals show retinitis pigmentosa, adiposity, genital hypoplasia, night-blindness, polydactylism and mental deficiency. This has since been called the Lawrence-Biedl syndrome and

the Bardet syndrome. The author adds the forty-eighth to the list of the reported examples of this syndrome. His patient was a girl, whose life age was fifteen years and eight months, and her mental age approximately five years. She was obese, weighing 194 pounds and had six toes on each foot. There was partial paralysis of the external rectus muscle of each eye, retinitis pigmentosa, and genital hypoplasia of moderate degree. It was formerly considered that this condition resulted from a disorder of the pituitary gland. More recently the tendency has been to regard a lesion of certain metabolic and genito-trophic centers in the floor of the midbrain as responsible. This is explained embryologically as dependent upon a genetic defect of the forebrain. Treatment with glandular extracts, chiefly thyroid and pituitary, has brought about improvement in some cases. This was true of the case reported.

Reviews

Human Heredity. By ERWIN BAUR, Professor of Heredity at the Agricultural Academy in Berlin, EUGEN FISCHER, Professor of Anatomy and Director of the Anatomical Institute at the University of Freiburg, Breisgau, and FRITZ LENZ, Professor of Racial Hygiene at the University of Munich. Translated by EDEN and CEDAR PAUL. 734 pages, 172 illustrations, and 9 plates. The Macmillan Company, New York City, 1931. Price, \$8.00.

This book is an English translation of the third edition of *Menschliche Erblichkeitslehre*, which was published in Munich in 1927, with supplementary material supplied during the preparation of the English version. The text is divided into five sections. The first section, by Baur, reviews briefly and clearly the general theories of variation and heredity. The second part, contributed by Fischer, treats of racial differences in mankind. From a consideration of the characters responsible for the differ-

ences in the external appearances of individuals the author proceeds to a discussion of racial origins and racial biology, and a description of the races of mankind. In classifying the so-called normal types of man, the author follows the usual German method of division into asthenic, pyknic, and athletic groups. Yet a considerable proportion of "normal" individuals fail to conform to any one of these three classes, so that this classification is far from satisfactory. The final three sections are all by Lenz and deal with morbid hereditary factors, with methodology in human heredity and with the inheritance of intellectual gifts, respectively. Many will find it impossible to subscribe to the definition of disease as "the state of an organism which is on the borderline of its capacity for adaptation," when such a conception causes the author to designate color blindness as an anomaly not coming within the category of disease. Practically all disease conditions

in which the hereditary factor is important in etiology are considered in this section and genealogical diagrams are presented for many of them. The importance of heredity in the etiology of neoplasms is recognized and discussed and here the genealogical tree of the remarkable cancer family described by Warthin is reproduced. Rather more weight is given to the factor of hereditary predisposition in the causation of rickets than is generally accepted. Distinction is made between *blastophthoria* and *idioknesis* in that the latter term is limited to hereditary alterations in the germ plasm induced by extrinsic agents. The work of translation has been unusually well done. The style is clear and free from the original idiom. This book should be read by all who are concerned with the medical and genetic aspects of the inheritance of disease.

Diagnostic Methods and Interpretations in Internal Medicine. By SAMUEL A. LOEWENBERG, M.D., F.A.C.P., Associate Professor of Medicine, Jefferson Medical College, Assistant Physician to the Jefferson Hospital, Visiting Physician to the Philadelphia General Hospital, the Northern Liberties Hospital and the Eagleville Sanatorium for Consumptives, formerly Assistant Professor of Physical Diagnosis at the Medico-Chirurgical College and the University of Pennsylvania, Philadelphia. Second Revised Edition. xxiii + 1032 pages. 547 illustrations, some in colors. F. A. Davis Company, Philadelphia, 1931. Price \$10.00 net.

This second edition of Loewenberg's *Diagnostic Methods* contains new material on the cardiac blood supply and innervation, massive pulmonary collapse, coronary thrombosis, hypertension and hypotension, sickle cell anemia, von Jaksch's anemia, agranulocytic angina, acute mononucleosis and the diagnostic importance of certain findings in the cerebro-spinal fluid. In order to incorporate some of this it has been necessary to interpolate a few new pages which are lettered in order to avoid complete re-paging. The well chosen illustrations and diagrams continue to be one of the valuable features of this work. The half-tones are not always satisfactorily reproduced but the

difficulty lies in the always present dilemma in choosing between a stock which will do justice to the cuts and one which will keep the volume within reasonable limits of size and weight. Many of the illustrations of gross pathology are of terminal stages or unusually severe manifestations. Perhaps they tell their story all the more emphatically because of this, but they should not be considered type forms. The reviewer is of the opinion that this book will gain in usefulness if, in the next edition, the space which is now devoted to very brief presentations of certain external and largely surgical conditions is utilized for a more complete exposition of the diagnosis of diseases of the internal organs. To illustrate this point, carcinoma of the breast is given seven lines of text and one and one-half pages of illustrations. Not much can be done with the diagnosis of carcinoma of the breast in seven lines, but in that brief paragraph the curious statement, presumably a typographical error, occurs that '*the lymphatic gland becomes enlarged*'. On the opposite page, polythelia, or polythelism, is designated *polythelin*, a form for which the reviewer fails to find authority. Since the diagnosis of carcinoma of the breast could not be presented adequately, it would have been more useful to have devoted this space to fuller treatment of some condition which presents a constant problem to the internist, as, for instance, bronchogenic carcinoma. In the brief discussion of this far from rare condition, no distinction is made, save in the section on radiography, between sarcoma and carcinoma, primary and secondary, in the lung. The general sections of the book rise to a high level of excellence. The difficult chapter on the examination of the respiratory system is especially well done, the many line drawings adding much to the clarity of the exposition and providing the necessary mechanistic explanation for many physical signs. In many respects this is an excellent textbook.

The Infant Welfare Movement in the Eighteenth Century. By ERNEST CAULFIELD, M.S., M.D., with a foreword by GEORGE FREDERIC STILL, M.A., M.D. (Cantab.), Hon. LL.D. (Edin.), F.R.C.P.

(London) xv + 203 pages 8 illustrations Paul B Hoeber, Inc, New York City, 1931 Price, \$2.00

"To all who are concerned in the welfare of children and in the steps by which the present almost over-anxious care of childhood has been reached, this book by Dr Ernest Caulfield will be of absorbing interest" Thus wrote G F Still in the Foreword Since in this day and age practically everyone is interested in the welfare of children, the appeal should be practically universal and the reviewer feels that such will prove to be the case The period dealt with is one in which there was an awakening of an individual and social consciousness of the value of child life Of the two decades, 1730-1750, it was stated that 75 per cent of all of the children christened in London were dead before they reached the age of five Children had been regarded as a necessary evil, and evidence of neglect, cruelty, and infanticide is readily attainable from contemporary sources Within the eighteenth century, however, there was seen at least the beginning of a different attitude toward the child Thomas Coram, William Cadogan, Jonas Hanway and George Armstrong are those about whom the story of this movement centers Although historical, this work never becomes a catalog of men or events, and it is enlivened by numerous direct quotations from original sources To a large circle, both within and without the profession of medicine, this book is heartily recommended

Diabetes Its Treatment by Insulin and Diet A Handbook for the Patient By ORLANDO H PERRY, A M, M D, F A C P, Professor of Diseases of Metabolism, Graduate School of Medicine, University of Pennsylvania, Physician in Charge of Departments of Diseases of Metabolism, Hospitals of the Graduate School of Medicine, University of Pennsylvania, and Philadelphia General Hospital, Consultant in Diseases of Nutrition and Metabolism, Shriners' Hospital for Crippled Children, Philadelphia Unit Fifth revised and enlarged edition 231 pages, illustrations and tables F A Davis Company, Philadelphia, 1931

The fifth edition of this handbook has been extensively revised The section on vitamins has been rewritten and enlarged, the subject of obesity and diabetic hygiene has been discussed in greater detail, and twenty-one pages of sample diets for those following the orthodox dietary rules of the Jewish faith have been added As is stated in the preface this is a book for the diabetic and not for the physician, but it is not intended to be a substitute for the physician The latter will find it an aid in giving the patient such a practical working knowledge of diabetes that his intelligent cooperation will be had It can be recommended safely for this purpose, but the physician should first become thoroughly familiar with its contents in order that no apparent differences in methods or explanations may appear

Pediatric Education Report of the Subcommittee on Medical Education, Section on Medical Service, White House Conference on Child Health and Protection 109 pages The Century Company, New York and London, 1931

The adequacy of the medical school teaching of pediatrics as judged by the opinion of the practicing physician, the proper position of pediatrics in the organization of medical schools, the minimum teaching facilities for pediatrics, and salient points to be presented in both undergraduate and graduate teaching are the subjects considered in this report The basic information used was obtained largely by the questionnaire method and consequently labors under certain limitations Nevertheless, teachers of pediatrics and medical school executives will find much that is thought-provoking and helpful in the data presented

On Phasic Introductory and Release Effects of the Cocaine Group on Vessel Preparations and an Attempt at a General Appraisal of Phase Effects By EDWARD RENTZ, Pharmacological Institute, Riga Translated and abstracted by LINN J BOYD, M D, F A C P, Professor of Pharmacology, New York Homeopathic Med-

ical College and Flower Hospital 146 pages Privately printed, 1931

Frog blood-vessel preparations were used in obtaining the basic data in a comparative study of the effects of cocaine and of a series of related substitution products as used in varying dilutions The resulting phasic effects are discussed in detail and their theoretical aspects considered in the light of what is known about similar reversible and cyclic modes of behavior induced by other substances Those interested in this field of investigation will find here a very large material and a reference list comprising 656 items

Permeabilitätsstudien an der Darmschleimhaut [Permeability of the Intestinal Mucosa] Von DOZENT DR HANS PATRATH, Assistant der Kinderklinik der Medizinischen Akademie in Dusseldorf 115 pages S Karger, Karlstrasse 39, Berlin, 1931. Price, Rm 8

This monograph is an experimental and clinical study of the permeability of the mucosa of the small intestine with special regard to the etiology of intestinal intoxication of infancy Apparatus and methods of investigation are described and the results obtained from several groups of substances under varying conditions are analyzed and presented

American Gastro-Enterological Association Transactions, 1930 xiii + 169 pages, numerous illustrations Paul B Hoeber, Inc, New York City, 1931 Price \$3 00

In this volume are gathered 27 scientific papers from the thirty-third annual meeting of the American Gastro-Enterological Association held at Atlantic City, New Jersey, May 5 and 6, 1930 Review of each of these is impossible The eminence of the authors in their respective fields and the selection of the topics as those most significant in present day gastro-enterology are a sufficient earnest of the worth of this collection of reports of original investigations

Anesthêsia geral pelo Protóxido de Azoto [Surgical anesthesia with nitrous oxide]

By Dr PEDRO AYRES NETTO Doctoral thesis from the Faculdade de Medicina de São Paulo 287 pages, 33 ill's Empresa Graphica de "Revista dos Tribunaes", São Paulo, Brazil, 1931

This thesis contains a detailed study of nitrous oxide as a surgical anesthetic, with survey of the literature and data derived from animal experimentation and personal observations of its clinical use A bibliography of 250 items is added

The Psychology of Insanity By BERNARD HART, M D (Lond), F R C P (Lond.); Fellow of University College, London, Physician in Psychological Medicine, University College Hospital and National Hospital, Queen Square, London Fourth edition xi + 191 pages The Macmillan Company, New York City, 1931 Price, \$1 25

This book was first brought out in 1912 and to the present edition, the fourth, but little new material has been added The relationship of the simple fundamental principles, as previously stated, to the structure of modern psychopathology has been made more evident by a new introductory chapter 19 pages in length and by occasional explanatory footnotes This book makes no pretense of being a complete treatise at any point Rather it is an *Einführung* leading the beginner by a logical approach and with proper emphasis upon historical development to the point from which the many independent schools of thought of the present day diverge For this reason those who seek a full exposition of the theories of Freud will not find them, for so far as Freudism is concerned this book aims to bring only certain selected aspects of Freud's teachings into relation with the lines of advance followed by other investigators, and thus to demonstrate that the conceptions of psychopathology have been built up in accordance with the rules and principles governing the development of other sciences To the medical student, physician, or to the general reader who desires background material or an introduction to the more obviously technical and partisan treatise, this small book can be fully recommended

College News Notes

REDUCTION IN REPRINT PRICE LIST

Attention of contributors to the *ANNALS OF INTERNAL MEDICINE* is called to the new price list of reprints appearing on the outside back cover of this journal, beginning with the November, 1931, issue. In quantities of four hundred or more a saving of from twelve and one-half per cent to thirty per cent has been effected and passed on to authors in reduced rates.

This saving is wholly due to a change in the paper stock used in *ANNALS* and in the reprints. Formerly two grades of paper, "antique" for ordinary purposes and enameled stock for illustrations, were used. The mixing of two grades of paper was not only expensive, but detracted from the appearance of the journal. For the November and subsequent issues, through the co-operation of the printers, "Andover plate" is used, making the stock uniform throughout the journal, and adding materially to its appearance.

Dr James D Bruce (Fellow and Governor for Michigan), Ann Arbor, Michigan, has been appointed by the Regents of the University of Michigan to the position of Vice President of the University in Charge of University Relations. In this new capacity Dr Bruce will supervise all of the University's extramural activities. His title at the time of his appointment to a vice presidency was Director of the Department of Post-Graduate Medicine, Member of the Executive Committee of the Medical School and Medical Adviser to the University Health Service.

Dr Edward S Calderwood, Dr Frederick T Lord and Dr Joseph H Pratt (Fellows), Boston, are members of a special Advisory Committee organized for the "purpose of studying the epidemiology, of promoting

prompt diagnoses, of encouraging and facilitating earlier and more general therapeutic use of concentrated serum, of improving methods for serum productions, of correlating the studies on serum production with the results following its clinical use, and of devising procedures for the future prevention, serum treatment and control of pneumonia."

The Commonwealth Fund of New York has made an annual appropriation of \$36,200 for three years to the Massachusetts Department of Health for this study. Various hospitals in different parts of the State will be selected to conduct a special service for pneumonia. Several laboratories will be chosen as pneumococcus type determination stations, and their technicians trained at the expense of the Fund. The Bacteriologic Laboratory of the State Department of Health will continue to make type determinations.

At the Second Annual Fall Clinical Conference of the Oklahoma Medical Society, held at Oklahoma City, November 2-5, many members of the College contributed as shown by the following report. Dr James B Herrick (Fellow), Chicago, and Dr Leroy S Peters (Fellow), Albuquerque, were among the distinguished guest speakers. Dr Herrick delivered an address on "Embolism as Seen by the Internist." Dr Peters delivered two lectures, one on "Treatment of Tuberculous Cavities," and one on "The Interpretation and Discussion of X-Ray Negatives of the Chest."

Other Fellows who gave addresses are indicated below. Unless otherwise mentioned, they reside in Oklahoma City.

Dr Arthur White—"Digestive Disorders Due to Lesions of the Stomach,"

Dr Lea A Riely—"Digestive Disorders Due to Lesions of Biliary Tract,"

Dr C J Fishman—"Intestinal Indigestion,"

Dr H W Butler—"Anomalies of Heart,"

Dr Ray M Balyeat—"Asthma,"

Dr Leila Andrews—"Functional Heart Disorders,"

Dr Wann Langston—"Management of Non-Valvular Myocardial Failure,"

Dr L J Moorman—"Modern Methods of Treatment of Advanced Pulmonary Tuberculosis,"

Dr John Heatley—"X-Rays of Lower Spine,"

Dr E S Lain—"Lesions of the Mouth and their Etiology,"

Dr. Tom Lowry—"Purpura"

Dr John F Kenney (Fellow), Pawtucket, R I, addressed the Rhode Island Medical Society at their last meeting, on "Recent Studies in Etiology of Appendicitis"

At the opening meeting of the Memorial Hospital Staff, Pawtucket, Dr Kenney read a paper on "Gastric Hemorrhage from other Causes than Ulcer"

Dr. Samuel M Feinberg (Fellow), Chicago, Ill, addressed the Will-Grundy Medical Society at Joliet, November 4, on "Allergy in Every-Day Practice"

At a meeting of the Royal Academy of Belgium held on June 27, Dr George R Minot (Fellow), Boston, Mass, was elected "Correspondent étranger de l'Académie royale de Médecine de Belgique"

Dr Soma Weiss (Fellow), Boston, Mass, addressed the New York Academy of Medicine at its Fourth Annual Graduate Fortnight, Beth Israel Hospital, New York, October 21, on "Paroxysmal Cardiac Dyspnea"

Dr William B Castle (Fellow), Boston Mass, Assistant Professor of Medicine at Harvard University Medical School and Associate Physician to the Thorndike Memorial Laboratory of the Boston City Hospital, is on leave of absence in Porto Rico where he is undertaking extensive studies

concerning anemia, sprue, uncinariasis and other conditions, and studying further the alteration of gastric function in anemia.

Dr Kelso A Carroll (Fellow), formerly of Tucson, Ariz, has accepted the position of Medical Officer in Charge of the Soldiers' Tubercular Sanatorium at Sulphur, Oklahoma

On the evening of October 6, Dr Robert M Moore (Fellow), Indianapolis, Ind, addressed the Vanderburgh County Medical Society at Evansville, on "Some Considerations of the Heart in Surgery"

The following Fellows of the College delivered papers before the Academy of Medicine, Parkersburg, W Va, November 5, as indicated

Dr Henry K Mohler, Philadelphia—"Auricular Fibrillation, An Analysis of 220 Cases,"

Dr Louis H Clerf, Philadelphia—"Bronchoscopy in the Diagnosis and Treatment of Pulmonary Disease"

At the annual meeting of the Montana State Medical Society, held at Bozeman this summer, Dr Harold W Gregg (Fellow), Butte, Mont, read a paper entitled "Notes on Early Montana Medical History"

Dr John Huston (Fellow), Milwaukee, Wis, was recently appointed Medical Editor of the Wisconsin Medical Journal

At the last regular meeting of the Denver Sanatorium Association Dr I D Bronfin (Fellow), Denver, was elected President for the coming year

Dr Frank Parsons Norbury (Fellow), Jacksonville, Ill, Consultant in Neuropsychiatry, Wabash Railway Hospital Service, delivered a paper entitled "The Importance of the Psychoses as Contributing to Disabilities Among Railway Employees" at the 49th annual meeting of the Wabash Railway Surgical Society at St Louis, Mo, November 2

Dr Oscar W Bethica (Fellow), Professor of Therapeutics in the Graduate School of Medicine of the Tulane University of Louisiana, delivered an address at Oxford, Miss, October 29, on "Recent Developments of Diagnosis in Chest Diseases"

A medical clinic on Pernicious Anemia recently held by Dr E Roland Snader, Jr (Fellow), Clinical Professor of Medicine at the Hahnemann Medical College of Philadelphia, was published in the October number of the Hahnemannian Monthly

Dr Frederic J Farnell (Fellow), Providence, R I, was elected a member of the Board of Directors of the American Prison Association, October 21, at Baltimore, Md

Dr E J G Beardsley (Governor and Fellow), Philadelphia, Clinical Professor of Medicine at the Jefferson Medical College, held a clinic at the Mercy Hospital, Altoona, Pa, October 27, which was attended by 150 physicians from Blair and adjoining counties

Dr Samuel A Levine (Fellow), Boston, Mass, addressed the New Haven Medical Society, October 7, on "The Clinical Significance of a Systolic Murmur"

Dr J W Torbett (Fellow), Marlin, Texas, was elected Vice-President of the Texas State Medical Association at the last meeting, and was made Chairman of the Committee for Cancer Control to carry on the educational work with the laity and medical profession this year

During the recent Ninth Annual Clinical Conference of the Kansas City Southwest Clinical Society, held in Kansas City, Mo, Dr Robert A Cooke (Fellow), New York City, spoke on "The Clinical Manifestation of Allergy," and conducted a clinic on "The Diagnosis and Management of Asthma" Dr A Morris Ginsberg (Fellow), Director of Clinics, conducted a class on "The Differential Diagnosis of Incipient Tuberculosis, Early Thyrotoxicosis and Effort Syndrome"

The following Fellows of the College conducted classes

Dr P T Bohan, Kansas City, Mo—Heart Therapy,

Dr Harry Jones, Kansas City, Mo—Miscellaneous Heart Disease,

Dr D D Stofer, Kansas City, Mo—Non-Infectious Heart Disease,

Dr Sam Snider, Kansas City, Mo—Pulmonary Tuberculosis—Recent Advances,

Dr J V Bell, Kansas City, Mo—Pneumothorax in Tuberculosis,

Dr W W Duke, Kansas City, Mo—Allergy in General Medicine,

Dr A C Clasen Kansas City, Mo—Nutritional and Deficiency Diseases

Dr Lindsay S Milne (Fellow), Kansas City, Mo, conducted a clinic on "Valvular Heart Disease," and Dr A Comingo Griffith (Governor and Fellow), Kansas City, Mo, gave a clinic on "Rare Medical Cases" Also, Dr W A Myers (Fellow), Kansas City, Mo, conducted a clinic on "Bladder Disturbances Associated with Lumbosacral Lesions"

Dr Louis H Clerf (Fellow), Philadelphia, read a paper before the Tri-City Pediatric Society, October 17, held at Philadelphia, entitled "Bronchiectasis in Children Bronchoscopic Observations"

Doctors Salvatore Lojano (Fellow), Marquette, Mich, Superintendent of the Morgan Heights Sanatorium, and Frank H Bartlett, Jr (Fellow), Muskegon, Mich, Medical Director of the Muskegon County Tuberculosis Sanatorium, were elected trustees of the Michigan Tuberculosis Association at the annual meeting of the organization on October 16

Dr Lojano was recently re-elected Secretary-Treasurer of the Michigan Sanatorium Association

Dr George L Lambright (Fellow) Cleveland, Ohio, gave an illustrated address before the Cleveland Academy of Medicine, October 16, on "Diverticulitis"

Dr Egerton Crispin (Fellow and Governor), Los Angeles, Calif, was elected

President of the Association of Resident and Ex-Resident Physicians of the Mayo Clinic and Mayo Foundation at the annual meeting held in Rochester, Minnesota, October 8-10

Dr Karl Rothschild (Associate), New Brunswick, N J, attended the International Neurological Congress at Berne, Switzerland, during the past summer. He read a paper entitled "Concussion of the Pons"

Dr Rothschild was elected a member of the American Psychiatric Association at its recent meeting held in Toronto

The following Fellows of the College are authors of articles appearing in the September, 1931, issue of the Journal of Laboratory and Clinical Medicine

Dr John R Williams (Fellow), Rochester, N Y—"Case Report of Extensive Atrophy of Subcutaneous Fat Following the Repeated Injections of Insulin" (abstracted in the November ANNALS),

Dr Miles J Breuer (Fellow), Lincoln, Nebr—"A Method for Urinary Urea"

The Interstate Postgraduate Medical Association of North America held its annual meeting at Milwaukee, Wis, October 19-23, under the presidency of Dr Henry A Christian (Fellow), Boston, Mass

The following Fellows of the College presented clinics as indicated

Dr Elsworth S Smith, St Louis, Mo
—Diagnostic Clinic (Medical),

Dr Harlow Brooks, New York, N Y
—Diagnostic Clinic (Medical),

Dr Henry A Christian Boston, Mass
—Diagnostic Clinic (Medical),

Dr W. McKim Marriott, St Louis, Mo—Diagnostic Clinic (Pediatric),

Dr James H. Means, Boston, Mass
—Diagnostic Clinic (Medical),

Dr John H Musser, New Orleans, La
—Diagnostic Clinic (Medical),

Dr Cyrus C Sturgis, Ann Arbor, Mich—Diagnostic Clinic (Medical),

Dr. Elliott P Joslin, Boston, Mass—
Diagnostic Clinic (Medical),

Dr Leonard G Rowntree, Rochester, Minn—Diagnostic Clinic (Medical)

The following Fellows of the College offered papers as indicated

Dr S F. Haines, Rochester, Minn—
"The Use of Iodine in Recurrent Exophthalmic Goiter,"

Dr. Elsworth S. Smith St Louis, Mo
—"Cardiac Irregularities Associated with Diseases of the Thyroid Gland,"

Dr S Marx White, Minneapolis, Minn
—"Mechanism and Transmission of Heart Murmurs with a Special Consideration of 'The Unimportant Murmur,'"

Dr. William S Middleton, Madison, Wis—"Syphilitic Aortitis,"

Dr William S McCann, Rochester, N Y—"Syndrome of Ayerza,"

Dr Charles A Elliott, Chicago, Ill—
"Circulatory Failure in Acute Infectious Diseases,"

Dr Louis Hamman, Baltimore, Md—
"Prognosis of Hypertension,"

Dr Harlow Brooks, New York, N Y
—"Coronary Thrombosis,"

Dr Henry A Christian, Boston, Mass
—"Aortic Lesions in Relation to Cardiac Physical Signs and Cardiac Function,"

Dr Warren T. Vaughan, Richmond, Va—"Allergic Diseases,"

Dr William Gerry Morgan, Washington, D C—"Does Peptic Ulcer Cause Permanent Disability?,"

Dr W. McKim Marriott, St Louis, Mo—"Infantile Paralysis,"

Dr James S McLester Birmingham, Ala—"Recent Advances in the Treatment of Nephritis,"

Dr Leonard G Rowntree, Rochester, Minn—"Water in Relation to Health and Disease,"

Dr William A White, Washington, D C—"Suggestions from Medical Psychology in the Field of General Medicine,"

Dr B R Kirklin, Rochester, Minn—
"Roentgenological Diagnosis of Early Tuberculosis,"

Dr Willis F Manges, Philadelphia, Pa—"Bronchial Obstruction, Partial

or Complete as shown by the Roentgen Ray Examination,"

Dr Paul A O'Leary, Rochester Minn—"Therapeutic Problems of Syphilis,"

Dr James H Meaus, Boston, Mass—"Significance of Hyper- and Hypometabolism,"

Dr Hugh S Cumming Washington, D C—Address,

Dr James E Paullin, Jr, Atlanta, Ga—"Different Forms of Jaundice and their Significance,"

Dr John H Musser, New Orleans, La—"The Medical Treatment of Gall Stones and Cholecystitis,"

Dr Cyrus C Sturgis, Ann Arbor, Mich—"Present Aspects of Treatment of Pernicious Anemia,"

Dr Elliott P Joslin, Boston, Mass—"Complications and Sequelae of Diabetes"

Dr Austin B Jones (Fellow), Kansas City, Mo, was recently elected President of the Internist Club, an organization of internists in Greater Kansas City

Dr Albert F Tyler (Fellow) Omaha, Nebr, is the author of an article entitled, "The Treatment of Epitheliomas by Physical Methods," which appeared in the November, 1931, issue of the Nebraska State Medical Journal

The following Fellows of the College are members of a Committee on Heart Disease, which was recently formed by the Arkansas Medical Society

Dr Arthur G Sullivan, Hot Springs,
Dr Arless A Blair, Fort Smith

The purpose of the Committee is "to acquaint the physicians of the State with recent advances in the diagnosis and treatment of heart disease by publishing articles in the state journal, presenting papers, and sponsoring scientific exhibits at the annual meetings"

At the recent annual meeting of the Kentucky State Medical Association, Dr Philip F Barbour (Fellow), Louisville, was elected President, and Dr C N Kavanaugh

(Fellow), Lexington, was elected Orator in Medicine

Dr Edwin C Ernst (Fellow), St Louis, Mo, acted as chairman of the Local Committee on Arrangements of the Radiological Society of North America, which held its seventeenth annual meeting in St Louis, November 30 to December 4

Dr Ray M Balyeat (Fellow), Oklahoma City, gave an illustrated address on "Etymology of Allergic Diseases" before the Tri-County Medical Society, October 1

Dr William Bernard Yegge (Fellow), Denver, addressed the Boulder County Medical Society, October 8, on "Diagnosis and Treatment of Gastric Ulcer"

During the months of October, November and December, under the auspices of the American Association of Social Workers and the American Association of Hospital Workers, a series of medical lectures for social workers was given at the Medical and Chirurgical Faculty Building, Baltimore, Md. The following Fellows of the College spoke on the dates indicated

Dr Henry M Thomas, Jr, October 19 and 23—"Bright's Disease, Diabetes, Pneumonia" and "Glands of Internal Secretion," Dr Thomas also spoke on December 21, on "Diseases of Old Age—Convalescence",

Dr Lewellys F Barker, November 2—"Nervous Diseases—Locomotor Ataxia, Paralysis Agitans, Psychoneurotic States",

Dr Victor F Cullen, November 10—"Tuberculosis,"

Dr Louis P Hamburger, December 15—"Minor Ailments—Aspects of Heart Disease"

The Hennepin County (Minn) Medical Society was addressed on October 5 by Dr Moses Barron (Fellow), Minneapolis, on "Purposes and Function of a Medical Society" Dr Barron also delivered an address before the Minnesota Academy of Medicine at Minneapolis, on "Importance

of Hepatomegaly and Splenomegaly in Differential Diagnosis"

At the annual meeting of the Medical Society of Pennsylvania October 5-8 at Scranton, Pa., the following officers were elected

Dr William H Mayer (Fellow), Pittsburgh, President,

Dr Charles Falkowsky, Jr (Fellow), Scranton, President-Elect,

Dr Walter F Donaldson (Fellow), Pittsburgh, Secretary

Dr Anton J Carlson (Fellow), Professor of Physiology at the University of Chicago, delivered the third annual William T. Bel-field Lecture of the Chicago Urological Society on October 29, in the auditorium of the Medical and Dental Arts Bldg Dr Carlson's subject was "Rejuvenation"

Dr Andrew B Rivers (Fellow), Rochester, Minn addressed the 46th semiannual meeting of the Eleventh Indiana Councilor District Medical Association, October 15, on "Cause of Hematemesis"

Dr Harry Gauss (Fellow), Denver, Colo., spoke on "Nervous Indigestion" at the sixty-first annual meeting of the Colorado State Medical Society, September 16 On October 27, he was a guest speaker at the forty-fifth annual meeting of the Colorado Homoeopathic Society, where he delivered an address on "The Basis of Diet"

Dr Gauss also was a guest speaker at the seventh annual meeting of the Colorado Hospital Association held jointly with the Colorado Dietetics Association, where he spoke on "The History of Diet in Fever"

Doctors Willis F Manges (Fellow), Philadelphia, E J G Beardsley (Governor and Fellow), Philadelphia, and H L Tonkin (Associate), Williamsport, addressed the Lycoming County (Pa) Medical Society at the Annual Clinic of the society at the Williamsport Hospital on November 13

Dr George A Harrop Jr (Fellow), Baltimore, addressed the Baltimore City Medical Society October 23 on "Treatment

of Addison's Disease with Adrenal Cortical Hormone"

Dr Howard R Hartman (Fellow), Rochester, Minn, recently delivered one of the second annual series of graduate lectures offered to physicians of Northampton, Pa, and surrounding counties under the auspices of the Easton Hospital Dr Hartman's subject was "Gastric Lesions and Gastric Hemorrhage"

Dr William H Mayer (Fellow), Pittsburgh, delivered an address, October 15, on "Fundamentals of the Mental Hygiene Problem" before the Cambria County Medical Society at Johnstown Pa

Dr Horton R Casparis (Fellow), Nashville, Tenn, discussed "Sinus Conditions in Childhood" before the Chattanooga and Hamilton County (Tenn) Medical Association, October 8

Lieut Comdr Franklin F Murdoch (Fellow) has been appointed Professor of Tropical Medicine at the George Washington University School of Medicine

Dr James H Hutton (Associate), Chicago, addressed the La Salle County (Ill) Medical Society, October 27, on "Recent Advances in Endocrinology"

Dr Bavard T Horton (Fellow), Rochester, Minn, spoke on "Buerger's Disease," before the Stephenson County (Ill) Medical Society on October 15

Dr Oscar W Bethea (Fellow), New Orleans, La, recently addressed the Iberville Parish Medical Society on "Recent Advances in Diagnosis"

"Histamine in the Study of Gastric Secretion and Disorders of the Stomach" was the title of an address delivered before the Kalamazoo Academy of Medicine, October 20, by Dr Charles I Brown (Fellow), Ann Arbor, Mich

Dr George I Lambright (Fellow), Cleveland addressed the Cleveland Academy

of Medicine, October 16, on "The Problem of Arthritis"

Dr Frank Smithies (Master), Chicago, Ill, addressed the Mahoning County (Ohio) Medical Society at Youngstown, October 27, on "Gastrorrhagia—Its Pathological and Clinical Significance and its Management"

Dr Frederick G Banting (Fellow), Professor of Medical Research at the University of Toronto Faculty of Medicine was the recipient of the honorary degree of Doctor of Science at the annual convocation of the University of the State of New York at Albany, October 15

The eighty-fifth semiannual meeting of the Southern California Medical Association was held at Hollywood, Calif, November 13-14, under the presidency of Dr Fred B Clarke (Fellow), Long Beach. The following Fellows of the College delivered papers as indicated below

Dr Samuel Ayres, Jr, Los Angeles—
"Use of the Patch Test in the Diagnosis of Contact Dermatitis,"

Dr Raymond G Taylor, Los Angeles—
"Some of the Causes of Failure in Treatment of Cancer"

Dr J Curtis Lyter (Fellow), St Louis, addressed the Randolph County (Ill) Medical Society, October 20, on diagnosis and treatment of diseases of the heart

On October 28, Dr James B Herrick (Fellow), Chicago, addressed the Medical History Club of the University of Illinois College of Medicine. Dr Herrick's subject was "Auenbrugger and Laennec"

Dr Harold W Palmer (Associate), Wichita, Kansas, spoke on "Hypothyroid States" before the October 20 meeting of the Sedgwick County (Kansas), Medical Society

Dr Sidney A Slater (Fellow), Worthington, Minn, was recently elected President of the Southwestern Minnesota Medical Association

Dr Thomas Grier Miller (Fellow), Philadelphia, addressed the Atlantic County Medical Society at Atlantic City, N J, October 9, on "Diagnosis and Management of the More Common Diseases of the Digestive System"

Dr Anthony Bassler (Fellow), New York, N Y, is Vice President of the New York Physicians' Club, a social organization which was recently organized

Dr Frank A Evans (Fellow), Pittsburgh, Pa, was one of the speakers on the program of the Allegheny County Medical Society held at Pittsburgh on October 27. Dr Evans' subject was "Infectious Mononucleosis"

Dr Ray M Balyeat (Fellow), Oklahoma City, Okla, addressed the Third District Medical Society at Lubbock, Texas, October 27-28, on "Allergic Migraine—Diagnosis and Treatment"

The following Fellows of the College addressed the forty-second annual meeting of the Association of American Medical Colleges, which was held in New Orleans, November 30-December 2

Dr Percy T Magan, Los Angeles—
"Rôle of the Medical School in the Development of Character in the Medical Student,"

Dr David J Davis, Chicago—"Cooperation between the College of Medicine of the State University and Other State Departments in Illinois,"

Dr Waller S Leathers, Nashville—
"Teaching of Preventive Medicine"

Dr Horton R Casparis, Nashville—
"Pediatrics Place in General Health Education Program"

Dr Kenneth S Davis (Fellow), Los Angeles, addressed the Los Angeles County Medical Association, November 5 on "Sarcoma of the Stomach"

Dr Charles A Elliott (Fellow), Chicago was among the speakers on the program of the fifty-seventh annual meeting of the Southern Illinois Medical Association No-

November 5-6 Dr Elliott spoke on "Management of Edema"

Dr. Chester S Keefer (Fellow), Boston, Mass., appeared on the clinical program of the joint meeting of the Suffolk District Medical Society and the Boston Medical Library on November 18. Dr Keefer's subject was "Importance of Infection in Arthritis"

Dr. Bernard Fantus (Fellow), Chicago, spoke before the joint meeting of the Saginaw and Bay County (Michigan) Medical Societies, October 28, on "Therapy of Colonic Stasis"

Dr James F Rooney (Fellow), Albany, N Y, addressed the eighth district branch of the Medical Society of the State of New York, October 1, on "Coronary Thrombosis"

Dr J H Elliott (Governor and Fellow), Toronto, has been appointed Professor of History of Medicine at the University of Toronto

Dr Henry S Houghton (Fellow), Dean of the State University of Iowa College of Medicine, is now on tour of the Orient as a member of a commission appointed to appraise and evaluate facts on foreign missions

Dr Joseph H Pratt (Fellow), Boston, has been appointed one of the associates of the Bingham Fund Associates for the Advancement of Rural Medicine, founded by Mr William Bingham, 2nd, of Bethel, Maine, for the purpose of giving aid to the development of medical practice in the State of Maine, and to provide a fund for the advancement of rural medicine

Dr. L. Winfield Kohn (Fellow), New York City, acted as Chairman of a meeting of the Baltimore Medical Club of New York, held at the New York Academy of Medicine Building on November 12

Dr J M T Finney, Professor of Clinical Surgery at Johns Hopkins School of Medicine, and Dr Julius Friedenwald (Fellow),

Professor of Gastro-enterology at the University of Maryland School of Medicine, were the guest speakers

Dr Gerald B Webb (Fellow), Colorado Springs, Colo., delivered a lecture on "The Prescription of Literature," October 21, in connection with a series of lectures on "The Care of the Patient" at the Harvard University Medical School

Dr Stewart R Roberts (Fellow), Atlanta, Ga., gave the second lecture of the series on October 28, his title being, "The Art and Human Nature"

Dr William W Duke (Fellow), Kansas City, delivered an address on allergy, October 13, in connection with the semiannual meeting of the Fort Worth Medical and Surgical Clinics and the meeting of the Northwest Texas District Medical Society

Dr Frank N Wilson and Dr Carl V Weller (Fellows) were among those who assisted in the graduate course arranged by the Department of Postgraduate Medicine of the University of Michigan Medical School and the Michigan State Medical Society, November 3-7. Diseases of the heart and circulatory systems were considered

Dr Weller has recently been elected president of the newly organized Michigan State Pathological Society

Dr Ralph Pemberton (Fellow), Philadelphia, addressed the Jackson County (Mich.) Medical Society at their meeting in Jackson, November 5, on "Arthritis"

The following appointments and promotions at the Long Island College of Medicine, New York City, were announced recently

Dr Frank B Cross (Fellow)—Clinical Medicine,

Dr Daniel M McCarthy (Fellow). Assistant Clinical Professor of Medicine,

Dr Paul I. Parrish (Fellow), and Dr Murray B Gordon (Fellow) promoted to Professors of Clinical Pediatrics

Dr II Sheridan Bakstel (Fellow), Jersey City, N J, has become Professor Emeritus of Preventive Medicine and Hygiene

Dr Egerton L. Crispin (Fellow), Los Angeles, and Dr Porter P. Vinson (Fellow), Rochester, Minn., were elected President and Treasurer, respectively, of the Association of Resident and Ex-Resident Physicians of the Mayo Clinic and Mayo Foundation at the thirteenth annual reunion of this body in Rochester, October 9

A series of public lectures in the interest of public health education will be offered under the auspices of the Medical Society of the District of Columbia during the fall and winter months. Dr James P. Leake (Fellow) of the U S Public Health Service, delivered the first lecture, October 25, on "Infantile Paralysis." Dr William A. White (Fellow), Washington, delivered the next lecture, November 8, on "Mental Health," and Dr Wallace M. Yater (Fellow), Washington, delivered the third lecture, December 6, on "Physical Fitness at Fifty."

Dr Henry C. Macatee (Fellow), Washington, was a speaker at a symposium on "When Winter Comes," in connection with these lectures, on November 22

Dr Louis H. Fligman (Fellow), Helena, State Director of the American Society for the Control of Cancer, and Dr Ernest D. Hitchcock (Fellow), Great Falls, have been appointed Chairman and a member, respectively, of a Committee of fifteen members of the State Medical Society of Montana for the purpose of formulating plans for an active campaign against cancer in that State

Dr Alfred Stengel (Master), Vice President of the University of Pennsylvania, Philadelphia, delivered an address on "Physical Diagnosis in Relation to Circulatory Conditions" before the meeting of the Association of Surgeons of the Pennsylvania Railroad, October 9, in New York City

GIFTS TO THE COLLEGE LIBRARY OF PUBLICATIONS BY MEMBERS

Acknowledgment is made of the receipt from Dr Edward J. Stieglitz (Fellow), Chicago, of his book "Arterial Hypertension," and of the receipt of a printed copy of a radio address entitled "Government Interference in the Home," delivered by Dr William Gerry Morgan (Fellow), Washington, D C, on Sunday, November 15, 1931, over the network of the National Broadcasting Company

The following gifts of reprints by members to the College Library are acknowledged

- Dr Linn J. Boyd (Fellow), New York, N Y—I reprint,
- Dr L. Winfield Kohn (Fellow), New York, N Y—I reprints,
- Dr William H. Kraemer (Fellow), Wilmington, Del—I reprint,
- Dr Philip B. Metz (Fellow), Washington, D C—I reprint,
- Dr Roy D. Metz (Associate), Detroit Mich—I reprint,
- Dr Oliver T. Osborne (Fellow), New Haven, Conn—I reprint,
- Dr Robert E. Ramsay (Fellow), Pasadena, Calif—I reprint,
- Dr Audley O. Sanders (Fellow), Palo Alto, Calif—5 reprints,
- Dr Walter M. Simpson (Fellow), Dayton, Ohio—I reprint,
- Dr Carl Vischer (Fellow), Philadelphia, Pa—I reprint,
- Dr Frank Wright (Fellow), Chicago Ill—I reprint

Dr John E. Gordon (Fellow), Detroit presented a paper on "Clinical Aspects of Poliomyelitis" before the Gratiot-Isabella-Clare County Medical Society, September 17

Dr James P. Leake (Fellow), U S Public Health Service, was one of the speakers at a symposium on the after-care of poliomyelitis under the auspices of the Bronx County (New York) Medical Society, September 16

Dr Ray W. Kissane (Fellow), Columbus Ohio, used as his title "Relation of Per-

sonal Habits to Adult Heart Disease" in an address before the Knox County Medical Society at Mt Vernon, Ohio, September 24

The Fayette County (Pa) Medical Society held its meeting at Uniontown, October 22 The following Fellows of the College conducted clinics

Dr. Henry L. Bockus, Philadelphia—Gastro-enterology,

Dr. George Morris Piersol, Philadelphia—Internal Medicine,

Dr. Harry B. Wilmer, Philadelphia—Allergic Diseases,

Dr. John Eiman, Philadelphia—Pathology

Dr. Elmer H. Funk (Fellow), Philadelphia, was recently appointed to the Sutherland M. Prevost Chair of Therapeutics, Materia Medica and Diagnosis at the Jefferson Medical College, succeeding the late Dr. Hobart Amory Hare

Dr. Robert B. Wood (Fellow), Knoxville, Tenn., addressed the Hamblen County Medical Society, recently, on "Metabolism and Hypertension"

Dr. Wood also addressed the Roane, McMinn, Monroe and Loudon County Medical Society in Lenoir City, September 3, on "Myocardial Failure"

Dr. Ray C. Blankinship (Fellow), Madison, Wis., addressed the Waupaca County Medical Association at Clintonville, September 24, on "Gastrointestinal Conditions"

Dr. Arthur L. Bloomfield (Fellow), Professor of Medicine, Stanford University School of Medicine, San Francisco, presented the opening lecture of the University of Southern California, September 15, his subject being, "Some Current Problems in Medical Education"

Dr. Lorenz W. Frank (Fellow), Denver, is the Constitutional Secretary of the Colorado State Medical Society

Dr. James G. Carr (Fellow), Chicago, addressed the Morgan County (Ill.) Medi-

cal Society, September 10, on "Rheumatic Heart Disease"

Dr. Ray G. Barrick (Associate), formerly Assistant Professor of Psychiatry at the State University of Iowa College of Medicine, has accepted an appointment at the Institute of Juvenile Research, Chicago Dr. Barrick will be in a charge of mental health work at the Illinois State Penitentiary, Assistant Professor of Criminology at the University of Illinois College of Medicine and Psychiatrist at the Joliet Child Guidance Clinic

Dr. Robert A. Cooke (Fellow), New York City, addressed the joint sessions of the Omaha-Douglas County (Nebr.) Medical Society and the American Congress on Physical Therapy, October 7, on allergy

Dr. Clarence H. Beecher (Fellow), Burlington, Vt., addressed the Grafton County (N. H.), Medical Society in a co-operative meeting with Dartmouth Medical School, October 9, on "Clinical Use of Purgatives"

Dr. Joseph H. Barach (Fellow), Pittsburgh, is the Director of the recently dedicated Falk Clinic of the University of Pittsburgh The Clinic was dedicated on September 28 Doctors Willard J. Stone (Fellow), Pasadena, and Dr. Alfred Stengel (Master), Philadelphia, were guests of honor and speakers at the evening meeting, Dr. Stone's title being "Certain Economic Phases of Medical Practice" and Dr. Stengel's title being "The Clinic and Medical Development" Dr. Barach spoke upon "Aims of the Falk Clinic".

Dr. Frederick G. Speidel (Associate), Louisville, Ky., participated in a symposium on diabetes conducted before the Jefferson County Medical Society, September 21

Dr. Hans Lissner (Fellow), San Francisco, addressed the 57th annual session of the Oregon State Medical Society at Eugene, Oregon, September 24, on "Recent Discoveries in Endocrinology and their Clinical Application"

Dr Horton Casparis (Fellow), Nashville, Tenn, Dr Francis H Smith (Fellow), Abingdon, Va, and Dr George B Lawson (Fellow), Roanoke, Va, all delivered papers before the Southwestern Virginia Medical Society at Marion, Va, September 24-25

At the 32nd annual meeting of the American Roentgen Ray Society at Atlantic City, September 22-25, the following Fellows participated as indicated

Dr Willis F Manges, Philadelphia—"Primary Carcinoma of the Lung—Roentgen Ray Diagnosis and Preliminary Report on Roentgen Therapy",
Dr Byrl R Kirklin, Rochester, Minn, (with Dr C M Moore)—"Benign Giant Cell Tumors"

Rear Admiral Edward R Stitt (Fellow), formerly Surgeon General of the U S Navy, was retired from active duty in the U S Navy October 1

Lieut Comdr John H Chambers (Fellow), Medical Corps of the U S Navy, has been transferred from the Public Health Service of Haiti to the Naval Hospital, League Island, Philadelphia

Dr Francis E Seneer (Fellow), Chicago, conducted a dermatologic clinic in connection with the Logan County Medical Society's meeting at Lincoln, Ill, September 24

Dr William W Duke (Fellow), Kansas City, Mo, delivered a paper on "Allergy as Related to General Medicine" before the Dubuque County (Iowa) Medical Society, September 8

Dr S Marx White (Fellow and President), Minneapolis, addressed the Linn County (Iowa) Medical Society at Cedar Rapids, September 10, on "Subacute Bacterial Endocarditis"

Dr Philip F Barbour (Fellow), Louisville, Ky, was elected President-Elect of the Kentucky State Medical Association at its annual meeting at Lexington, September 7-10

Dr Stuart Pritchard (Fellow), Battle Creek, and Dr James D Bruce (Fellow), Ann Arbor, were among those chosen by Governor Brucker as members of an Advisory Commission to coordinate child welfare work in Michigan

Dr Frederick G Banting (Fellow), Toronto, was one of the speakers at the annual convocation of the University of the State of New York, held in the State Education Building, Albany, October 15-16

Dr I M Rabinowitch (Fellow), Montreal, participated in the symposium on the liver and spleen, held under the auspices of the Vermont State Medical Society at Rutland, October 8-9

Dr Louis F Jermain and Dr John J McGovern (Fellows), both of Milwaukee, were the recipients of the gold seal of the Wisconsin Medical Society at its recent annual meeting. The gold seal is an honorary award presented annually

Dr Otho R Fiedler (Fellow), Sheboygan, was installed as President of the Society for the coming year

OBITUARIES

DR BRADFORD CHURCHILL
LOVELAND

Dr. BRADFORD CHURCHILL LOVE-
LAND (Fellow), Syracuse, N Y, died
June 25, 1931, of myocarditis, age
sixty-nine years

Dr. Loveland was born at Newark,
N Y, and attended Newark Acade-
my, Susquehanna University, and
later the University of Michigan Med-
ical School, from which he received
the degree of Doctor of Medicine in
1888. He pursued postgraduate study
at the New York Post-Graduate Med-
ical School. He was a lecturer on
medical jurisprudence at the Syracuse
University School of Law from 1917
to 1927. His practice was limited to
neurology and psychiatry. During
1898-1899 he served as Medical Su-
perintendent of the Clifton Springs
Sanitarium. Soon thereafter he went
to Syracuse, where he became Neu-
rologist for the Hospital of the Good
Shepherd and the Syracuse Free Dis-
pensary. For several years he served
as Chief of the Bureau of Psychiatry
of the Syracuse Department of
Health, and was Neurologist to the
Syracuse University Hospital. Dr.
Loveland was a member and trustee
of the Syracuse Academy of Medi-
cine, a member of the Onondaga Med-
ical Society, a member of the New

York State Medical Association, a
Fellow of the American Medical As-
sociation, and had been a Fellow of
the American College of Physicians
since April 15, 1920. He was the
author of a considerable number of
articles published in various medical
journals.

DR THEODORE LEACRAFT
HEIN

Dr THEODORE LEACRAFT HEIN
(Associate), New York City, died
September 25, 1931 of heart disease,
aged 52 years.

Dr. Hein was a graduate of the Col-
lege of Physicians and Surgeons of
Columbia University, 1905. He did
postgraduate study in medicine at St.
Bartholomews, London, Charité of
Berlin, and at the Allgemeines Kran-
kenhaus of Vienna. He was formerly
instructor at the New York Post-
graduate Hospital, and assistant in the
Vanderbilt Clinic and the Stuyvesant
Polyclinic. At the time of his death
he was physician-in-charge to the
Queens Plaza and Ridgewood Clinics,
Department of Health. Dr. Hein was
a Fellow of the American Medical
Association, a member of the Medical
Society of the County of New York,
and had been an Associate of the Col-
lege since 1921.

Quinidine Therapy in the Treatment of Cardiac Irregularities Due to Hyperthyroidism*†

By J P ANDERSON, M D, F A C P, *Cleveland, Ohio*

QUINIDINE sulphate has rightfully earned a permanent place in the treatment of cardiac irregularities, especially those which are secondary to hyperthyroidism. The heart rhythm naturally tends to return to normal after thyroidectomy alone but by the addition of quinidine therapy the number of restorations to normal rhythm can be increased greatly.

The percentage of cases in which the heart rhythm returns to normal after thyroidectomy alone depends chiefly on the following factors: (1) the duration of the irregularity of the heart rhythm previous to operation, (2) the degree of arteriosclerosis and myocardial degeneration, (3) the age of the patient; (4) complications, such as focal infections.

In 1927, I reported a series of 75 cases of hyperthyroidism in nearly all of which auricular fibrillation had been present for a long time, and in several cases extensive cardiac failure had been present for several years. Our follow-up records showed that in only 32 per cent of these cases did the rhythm return to normal. Later in

the same year I reported another series of 75 cases which included all patients who had shown any auricular fibrillation while in the hospital. Sixty per cent of this second series acquired normal rhythm. Quinidine was used three times. In a later series of cases the normal rhythm was restored in 66 per cent.

At that time quinidine was not being used directly after operation, and the difficulty of instituting treatment a few weeks later led to the omission of its use in a large number of cases. Also, it was found that our attempts to restore normal rhythm a few weeks or months after thyroidectomy frequently met with failure. This fact led to the institution of quinidine therapy while the patient was still in the hospital. At first it was administered on the sixth or seventh postoperative day, and no embolic accidents resulted from its use. However, by that time the patient was out of bed and ready to go home and did not wish to remain in the hospital for two or three days longer in order to undergo treatment for the heart.

We then tried instituting quinidine therapy during the decline of the postoperative reaction, that is, on the third or fourth postoperative day. The good results of this experiment would seem to indicate that this is the best time to

*Presented at the Baltimore meeting of the American College of Physicians, March 26, 1931.

†From The Cleveland Clinic, Cleveland, Ohio.

institute treatment as the patient is still in bed and his stay in the hospital need not be prolonged after he is able to be up

No attempt is made to restore the heart to a normal rhythm before operation because it is seldom successful, and if it does succeed, auricular fibrillation is likely to recur at the time of the operation. For this reason quinidine is seldom used after a first lobectomy.

At the Cleveland Clinic we have adopted the following plan of management of patients with hyperthyroidism in whom abnormal heart rhythm is present.

All patients in whom auricular fibrillation is still present on the third post-operative day are reported. A test dose of quinidine is administered to these patients and if no ill effects are noted they receive 5 grs of quinidine sulphate every four hours, day and night, for twenty-four hours. The pulse is counted before the administration of each dose and if the rhythm is found to be regular, medication is discontinued. If no improvement is noted after twenty-four hours treatment, 5 grs of quinidine are given every three hours for twenty-four hours and then every two hours for twenty-four hours, and occasionally for forty-eight hours.

In the majority of cases normal rhythm will be restored after a few doses, but occasionally two or three days' treatment will be necessary. In one case we found no change after the third day, and treatment was continued on the fourth day. Two hours after the last dose of quinidine had been administered, normal rhythm was restored.

In the case of one of our patients,

a woman 46 years of age, a very interesting result from the use of quinidine was noted. Symptoms of hyperthyroidism had been present for two years previous to thyroidectomy. The thyroid tissue showed diffuse hyperplasia. After thyroidectomy had been performed, the general condition improved greatly but the patient was nervous and her heart continued to fibrillate. The administration of digitalis did not slow the ventricular rate to normal although it reduced it from 130 to 100. The patient's basal metabolic rate was +23, suggesting that residual hyperthyroidism was present. The administration of iodine had no effect on the heart action. Inasmuch as there was no recurrent enlargement of the thyroid gland, quinidine therapy was instituted with the result that the heart rhythm became normal, the nervousness disappeared, and the patient was able to return to work. Since that time, a year ago, there has been no recurrence of symptoms.

A very few patients are sensitive to quinidine. In one of our recent cases, the patient experienced a great deal of distress during one night after her third dose of 5 grs of quinidine. She became dyspneic, nauseated, flushed, perspired a great deal, and experienced fear of death. It can not be stated definitely whether this condition was due to the effect of the quinidine or to a pulmonary embolus but the fibrillation persisted, and the patient refused further treatment.

In the case of another patient quinidine therapy had to be discontinued on account of nausea and vomiting. Its administration was attempted a second time with a similar result.

The question is frequently asked—will auricular fibrillation recur after the heart rhythm has been made regular by the administration of quinidine? We know of only one case in which there was a recurrence of auricular fibrillation after a thyroidectomy had restored the heart rhythm to normal,

in death. For several days the temperature varied between 103° and 105.5° and the pulse rate varied between 130 and 160, but at no time was any auricular fibrillation present.

In table I is shown the effect of thyroidectomy on auricular fibrillation.

Table II shows the results of the use

TABLE I

	Regular after thyroidectomy	Irregular after thyroidectomy
Series I	24	51
75	32%	68%
Series II	45	30
75	60%	40%
Series III	112	73
185	60.5%	39.5%
Series IV	26	31
57	45.7%	54.3%

TABLE II

	Treated with quinidine	Regular after quinidine	Irregular after quinidine
	late	10	6
	16	60%	40%
	prompt	22	1
	23	96%	4%

and in the group in which quinidine therapy was instituted there has not been any recurrence of auricular fibrillation.

In one case, a patient was given quinidine on the fourth postoperative day and the heart rhythm became regular. The following day auricular fibrillation was again present. Upon inquiry it was found that only a lobectomy had been performed. It is my opinion that if auricular fibrillation recurs after quinidine has been administered postoperatively, residual or recurrent hyperthyroidism may always be suspected.

In another case the patient was given quinidine about six months after a thyroidectomy had been performed. After the third day of treatment the heart rhythm was found to be restored to normal. A few months later an abdominal operation was performed, followed by a general peritonitis resulting

of quinidine in a series of cases with persistent auricular fibrillation after thyroidectomy. In sixteen cases quinidine therapy was instituted during a period of from several weeks to several months following operation, and of this group the normal heart rhythm was restored in 60 per cent of the cases while in 40 per cent the rhythm remained irregular. In 1930 a follow-up record was made of 57 cases following thyroidectomy. Quinidine therapy was instituted promptly in the treatment of 23 patients resulting in the restoration of the normal heart rhythm in 96 per cent.

When auricular fibrillation is still present after the fourth postoperative day, it usually persists unless quinidine therapy is instituted, and our experience has demonstrated that better results are obtained if quinidine is given during the decline of the postoperative reaction.

AURICULAR FLUTTER

In my experience the complication of auricular flutter associated with hyperthyroidism has been encountered only three times, and in two of these cases auricular fibrillation and auricular flutter were present alternately. Of the three patients who were treated with quinidine, normal heart rhythm was restored in two cases but not in the other, although a very thorough course of quinidine therapy was given. Auricular fibrillation was present in the latter case and after the administration of quinidine the heart rhythm became regular but the pulse rate remained at about 100. This condition was unusual, as the pulse rate after the heart rhythm has been restored to normal is usually about 80. An electrocardiogram showed a flutter which la-

ter was unaffected by four days' treatment with quinidine.

CONCLUSIONS

1. Quinidine sulphate is a very useful drug for the restoration of a normal cardiac rhythm if a thyroidectomy alone fails to achieve this result.
2. Observations over several years show that the maximum benefit is obtained when the drug is given on the third or fourth postoperative day.
3. A very few patients are sensitive to quinidine, thus prohibiting its use in such cases.
4. By adding quinidine therapy after thyroidectomy when auricular fibrillation is still present, a normal cardiac rhythm will be restored in about 96 per cent of cases.

Tachycardia*†

BY CHAS W BARRIER, M D, *Fort Worth, Texas*

TO a noted cardiologist of the previous generation, paroxysmal tachycardia was merely a clinical curiosity. To the few who have attacks prolonged into weeks and even years and who suffer acute heart failure when an extra burden such as a cold and cough is put upon them, it is a tragedy.

I am limiting my subject to auricular and nodal tachycardia. The literature does not indicate the number subject to these attacks. This paper is based upon a study of twenty-six proven cases occurring in about four thousand general admissions in three years. If to this twenty-six are added those who gave histories of paroxysmal acceleration, but who were without electrocardiograms, the incidence of paroxysmal tachycardia would be higher than is generally thought.

ETIOLOGY

Experimentally, Lewis¹ has produced attacks by stimulation of the vagus nerve and by ligating the coronary artery.² Boorman⁴ destroyed the sinus node with radon, but this was often eventually followed by a rhythm

simulating a typical sinus rhythm. Bouchut³ reports a case with an infarct in the region of the sinus node. Clinically, Major⁵ found acute and chronic myocarditis in the auricle of a person dying in an attack, and Anderson⁶ reports auricular tachycardia as a complication of diphtheria. Attacks are not unusual in cases of mitral stenosis, and they are likely to occur in the course of heart failure from various causes. Kern⁷ reports a case occurring on inflation of the Fallopian tubes with air. It is interesting to conjecture that the attack was due to air embolism of the coronary artery, basing our conjecture upon the frequency of tachycardia after occlusion and of the occurrence of coronary embolism when air enters the circulation.

An important exciting cause of tachycardia is drugs, chief among which is digitalis, as pointed out by Luten.⁸ Howard⁹ calls our attention to the great danger of excessive digitalis producing a coexistent auricular and ventricular tachycardia. Galli,¹⁰ contrary to the experience of Lewis, insists that atropine can excite paroxysms. Adrenalin will frequently cause attacks in susceptible patients. Terrell¹¹ has observed nodal attacks after ephedrine in an asthmatic who had not previously had attacks. Numerous other drugs, as well as mineral salts, may provoke

*Presented at the Baltimore meeting of the American College of Physicians, March 27, 1931.

†From the Harris Clinic Hospital, Fort Worth, Texas.

them In spite of the efficacy of quinine in stopping attacks, Korns¹² labels it as an excitant of tachycardia.

The great majority suffering from tachycardia are free of cardiac pathology. Cair¹³ stresses its occurrence among the nervous type, and Thomas¹⁴ reports cases occurring in persons subject to other neuroses such as migraine.

Two of my cases had early exophthalmic goiter, one had rheumatic endocarditis, a few had mild hypertension, and several fell in the sclerotic heart group, but most were without heart lesions. Two were conspicuous because of their athletic prowess. Yet, even these had marked nervous instability, one of them blushing, trembling and turning giddy when called on in class.

Colgate¹⁵ reports cases occurring in early infancy, and while cases occur at any age, the literature would indicate the prevalence of tachycardia in the fifth and sixth decade. My cases fall roughly into two age groups, the first is that of adolescence in which the individuals have excessive variability of their sinus rate and an increased emotionality suggesting in many a degree of hyperthyroidism. The other group consists mostly of women about the menopause who are often overworked, poorly nourished, suffering from the effects of purgatives and flatulence, and frequently from migraine attacks. In both, attacks are precipitated most often by unusual exertion or emotions.

MECHANISM

Lewis¹⁶ teaches that the mechanism of an attack is repeated ectopic systoles, a different mechanism from flutter which is a circus movement. Colgate¹⁵ observed cases in which it was difficult

to tell the difference in electrocardiograms between cases of tachycardia and flutter. He concluded that the mechanism of tachycardia was a circus movement varying only in degree from that of flutter. One would conclude from Crawford's¹⁷ case in which there was a shift of the pacemaker from the sinus to the lowest part of the A-V node that the attacks are neurogenic. Willius dismisses the idea that toxins make these hearts unusually susceptible to nervous influences. The view of Otto,¹⁸ arrived at from the action of drugs on the onset and arrest of attacks, that the mechanism is a circus movement, seems the most plausible.

PROGNOSIS

To Willius¹⁰ the prognosis depends upon the underlying heart pathology and upon the rate and duration of the attacks. Many texts speak of the prolonged attacks ending in congestive heart failure and death. Carr¹³ believes that death is a rare termination. One of my patients who had mitral stenosis and a crippled myocardium entered the hospital on the thirteenth day of an attack, cyanotic, with a bloody sputum and general anasarca. Recovery took place. Another who endured attacks lasting for months with a rate of about 160 without trouble except for a limitation of his efforts, developed acute congestive heart failure after a cold and cough, and death was imminent for days. The usual rate of 160 increased to 200 and the mechanism from auricular to nodal.

Prognosis, however, does not concern itself so much with mortality as with incapacity. This incapacity in short attacks varies from concern over

the rate and unpleasant palpitation to more serious symptoms such as cardiac pain,²⁰ syncope and convulsions,²¹ but as a rule the general comfort and lack of dyspnea are striking when the excessive rates are considered. Nodal tachycardia causes more symptoms than an auricular attack of the same rate due, no doubt, to poorer filling of the ventricle and the contraction of the auricle against a closed valve. One patient with a mild exophthalmic goiter, B M R +35, experienced no real inconvenience from a sinus rate of 150, but complained of severe heart pains, violent palpitation, nausea, vomiting, and fainting at a sudden onset of nodal tachycardia with a rate of only 160.

In some patients, prolonged duration is the chief disturbing factor. Most authors report the time as only a few minutes and at the longest as only a matter of weeks. Cohn speaks of attacks extending into years, and Gilbert²² reports a case which he considered permanent. One of my cases lasted seven days, one thirteen days, one six weeks, one three years save for one thirty minute interval, and one case for the past six years has been in permanent tachycardia except when under the effects of digitalis. The case lasting three years had for years been subject to frequent short attacks in which there was fainting, but after the onset of permanent tachycardia the rate dropped to between 160 and 180 and she lived in comparative comfort. The other case in which the tachycardia was permanent was comfortable while at quiet occupations, but on strenuous exercise the rate would rise to above 200 with distressing dyspnea.

These patients with prolonged attacks, unless victims of obvious heart lesions, have suffered no cardiac deterioration from the rate.

DIAGNOSIS

The characteristics of paroxysmal auricular and nodal tachycardia upon which a diagnosis is made clinically are the abrupt onset and arrest, repetition of attacks, constancy of the rate throughout an attack, the much quoted observation of Feil²⁴ of the absolute regularity of rhythm, and the effect of vagus stimulation in arresting an attack.

It is not unusual, however, for auricular attacks to begin at rates above 180 and finally drop to 140 or less. The rate may increase because of exercise or atropine, and the rhythm may be irregular due to vagus effect or drugs, digitalis in one case producing a bigeminy, and a fast sinus rate may unnoticedly pass into an auricular tachycardia of the same rate by a gradual shift of the pacemaker.

TREATMENT

Treatment consists in removing the cause, arresting and preventing attacks. Two of our cases were permanently cured by iodine and thyroidectomy. Most attacks are short and end spontaneously. Often rest, chloral and bromides are necessary. All stimulants such as camphor should be prohibited.

Vagal stimulation has been the most popular mode of arrest. Fiessinger²⁵ has obtained this end by depriving the patient of air causing forced respiration. Wolffe²⁶ stops attacks by intravenous calcium, the action being very similar to quinidine, while Steppe²⁷

has made use of the vagotonic action of cholin. Wilson²⁸ publishes cases showing arrest by intravenous digitalis. Eakin²⁹ would use digitalis with caution in tachycardia unless the attack is known to be supraventricular because of its danger in ventricular tachycardia, especially in the presence of coronary occlusion.

Bodin³⁰ first used quinidine, showing that it would stop some attacks, while only slowing the rate in others, and Ihescu³¹ publishes a case in which the rate was slowed to the normal rate without a change of mechanism. Sprague³² believes half the cases can be arrested by quinidine and shows its value in preventing attacks.

We have treated eight patients in repeated attacks with digitalis either with massive doses by mouth or intravenously. Arrest was obtained in six cases, and was felt in all probability to be due to the digitalis. In ten cases we have used quinidine sulphate either by mouth or vein and arrested attacks in nine. There were five of these cases that responded both to digitalis and quinidine. Two patients, one because of apparently permanent tachycardia or frequent attacks, were rationed on quinidine for a year. Attacks were certainly warded off, but the dose had to be increased from a start of six grains a day to twenty-one. Even at this dose attacks appeared and the patients complained so vehemently of the drug that it was withdrawn. These two cases and one other case of permanent tachycardia were kept on digitalis for the greater part of two years. Though large doses, four to six grains a day, were often required, the results on the whole were more satisfactory.

MODE OF ACTION OF DRUGS

As the mode of action of drugs in stopping attacks is of supreme interest, careful records of the action of digitalis and quinidine given intravenously were made in the following cases.

Case I A woman of thirty-nine, whose examination, made later, revealed no finding varying from normal except a blood pressure of 148, entered the hospital one and one-half hours after the onset of an attack, in circulatory collapse. She had a nodal tachycardia, rate 255. Three hours after the onset 8 cc of digalen were given by vein, and in seven minutes the rate was slowed to 220. After a second dose of 6 cc, sinus mechanism was restored, rate 90. (See figure 1.)

Case II A vigorous man of thirty-two without any heart lesion came to the Clinic because of attacks of tachycardia which had come at frequent intervals since age sixteen. They were usually ushered in by exertion or emotion and lasted from one to fourteen hours. It always required a period of rest before cessation of an attack.

On the second morning an attack of nodal tachycardia, rate 260, was induced by ten minutes of vigorous exercise. This attack was allowed to subside spontaneously. After about half an hour the rate had slowed gradually to 200. In another hour the rate suddenly dropped from 200 to 90. During the next twenty minutes there was frequent repetition of the fast rhythm, but finally the slow rate was established.

On the next morning another attack was induced. In one minute after the injection of only 0.05 gram of quinidine sulphate the rate had appreciably slowed. A tracing one minute after an injection of 0.1 gram of quinidine sulphate showed a sinus rhythm with a rate of 150, which in four minutes had dropped to 110. The total dose was 0.25 gram, and the total time thirty-four minutes. (See figure 2.) The mode of arrest was quite a contrast to the spontaneous one. The total dose might have been given at one time and no doubt arrest would have been sudden.

A third attack was induced the next morning. In one minute after 5 cc of digifolin, the rate had dropped from 255 to 240 and at the end of seven minutes to 195, and at the end of thirty minutes after a total dose of 20 cc the rate was 180 and markedly irregular. Three minutes later normal rhythm ensued before inversion of the T-wave. (See figure 3)

Case III A woman of twenty-one without a heart lesion came for examination in 1928 saying that five years before she had had her first attack of fast heart. These attacks became more frequent and extended, so that for the last three years she had been in a constant attack. Nodal tachycardia, rate 160, was found. Quinidine sulphate caused a normal rhythm of 100. As this gave so much relief she was kept

on quinidine for the year of 1928. At first six grains a day were sufficient, but by the end of the year twenty-one grains were necessary and attacks became so frequent and the effects of the large doses so annoying that quinidine was discontinued.

It was then found that digitalis in large doses would ward off attacks, and for 1929 and part of 1930 she stayed on digitalis. While attacks occurred she felt that her condition was distinctly better than when on no treatment and on quinidine, but in June, 1930, she stopped digitalis and found that she was free of attacks unless she lost sleep or overworked. When attacks occurred, they were more violent and had to be stopped with quinidine.

Five hours after the onset of an attack on January 18, 1931, she entered the hospital before any treatment. Nodal tachycardia,

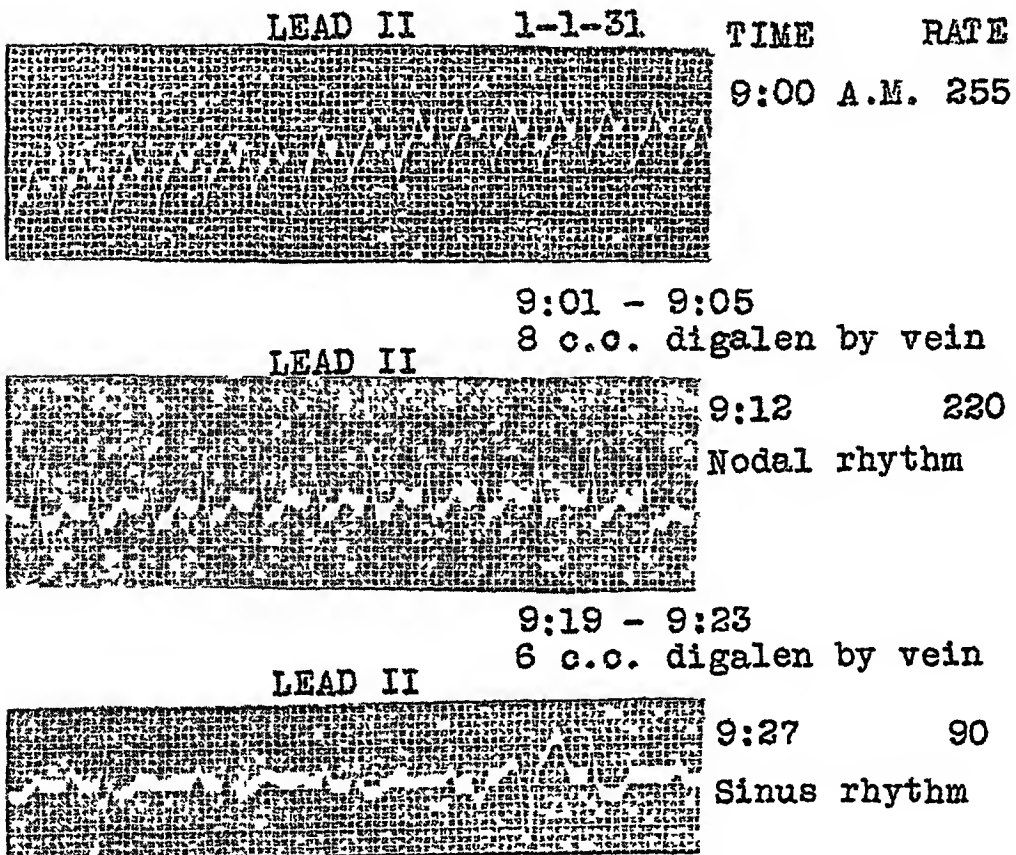


FIG 1 Nodal tachycardia Arrested with digitalis

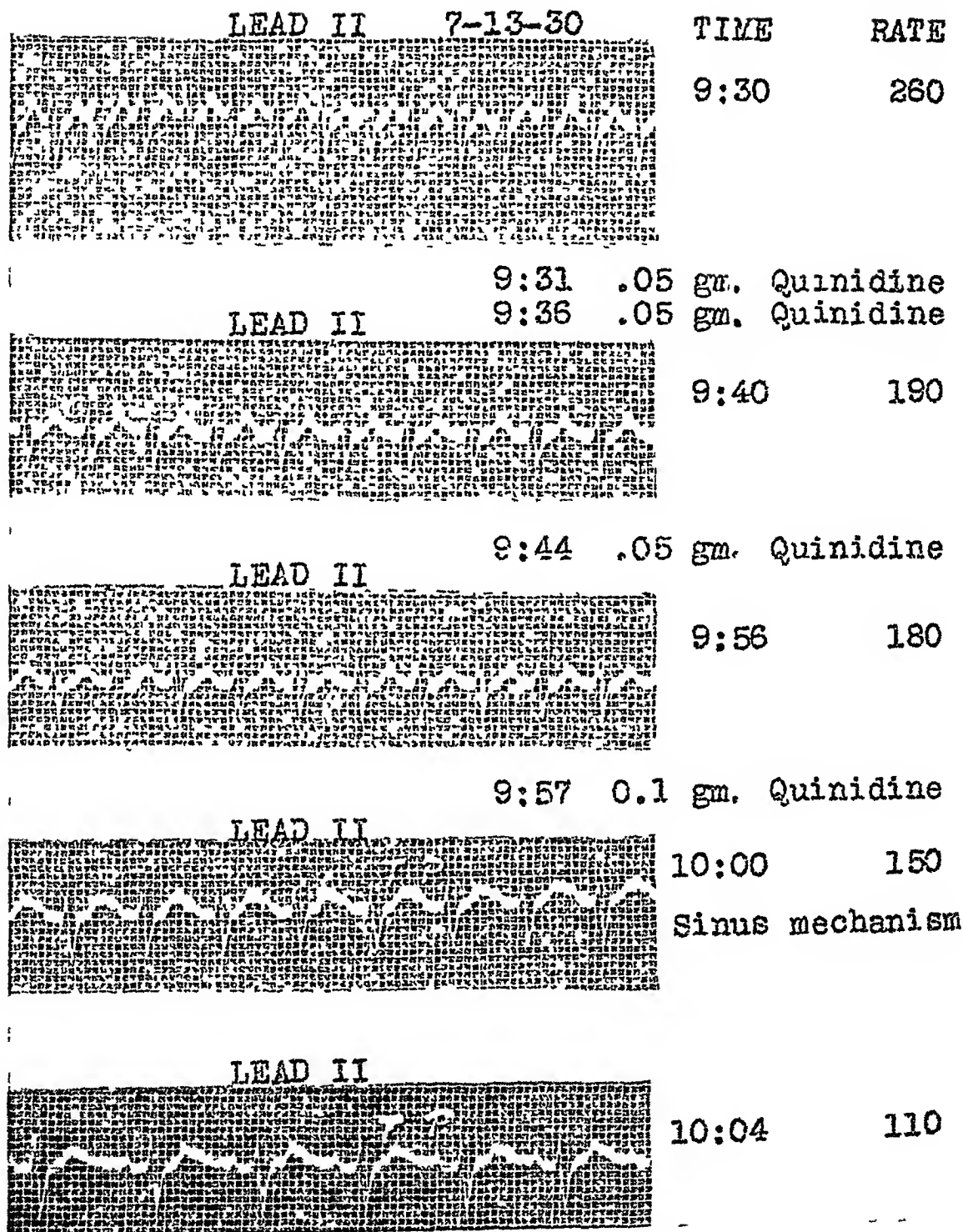


FIG 2 Nodal tachycardia Tracing every three minutes, string under constant vision

rate 195, was present Three minutes after the injection of 0.2 gram of quimidine, normal rhythm resulted, rate 145 In forty minutes this had gradually slowed to 110 (See figure 4)

Nine days later she again entered the hospital, twelve hours after the onset of

Case II A boy of twenty-one, robust in every respect and without heart lesion, first came under observation four years ago His physician had records showing a tachycardia for the previous two years His was an auricular tachycardia, rate 160 to 190 Repeated efforts with quimidine failed

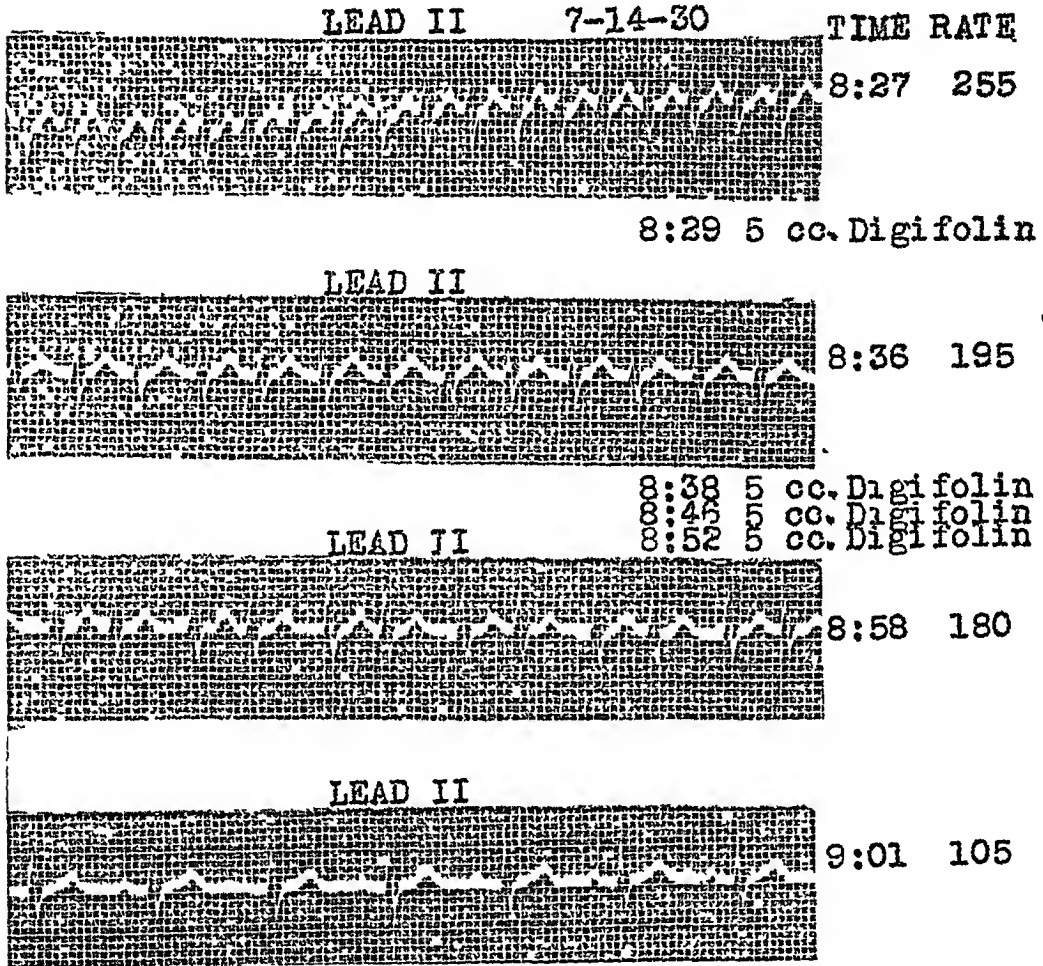


FIG 3 Nodal tachycardia Digitalis Tracings every three minutes, string under constant vision

tachycardia, the rate being 180 Three doses of 4 cc each of digalen were given by vein in thirty-three minutes After the first dose there was a gradual slowing so that after fifty minutes the rate had dropped to 125, but nodal rhythm persisted Seven minutes later there was a sudden drop of rate to 50, irregular, but of sinus mechanism (See figure 5)

to effect an arrest Since his first admission he has been in tachycardia except when under digitalis It took about 25 to 30 cc of the tincture to arrest an attack, but the tachycardia reappeared in about five days if digitalis was left off Large maintenance doses were required and even then after a few days a fast sinus arrhythmia with relapses to auricular tachycardia occurred

After leaving off digitalis for three weeks he was admitted in an attack, rate 170, of two weeks duration. Eight-tenths of a gram of quinidine sulphate was given in divided doses by vein over a period of one and one-fourth hours. Though unmistakable evidence of intoxication was present, sinus mechanism was not established, but the rate was slowed. Vagal stimulation then caused

After leaving off digitalis for a month he again entered the hospital in auricular tachycardia, rate 145, duration three weeks. After exercise the rate rose to 160. He was then given atropine, $1/25$ grain. During the next thirty-seven minutes he was given 8 cc of digalen and $4/150$ grain of atropine. Ten minutes later he had a sinus mechanism, but in fifteen minutes more this had changed

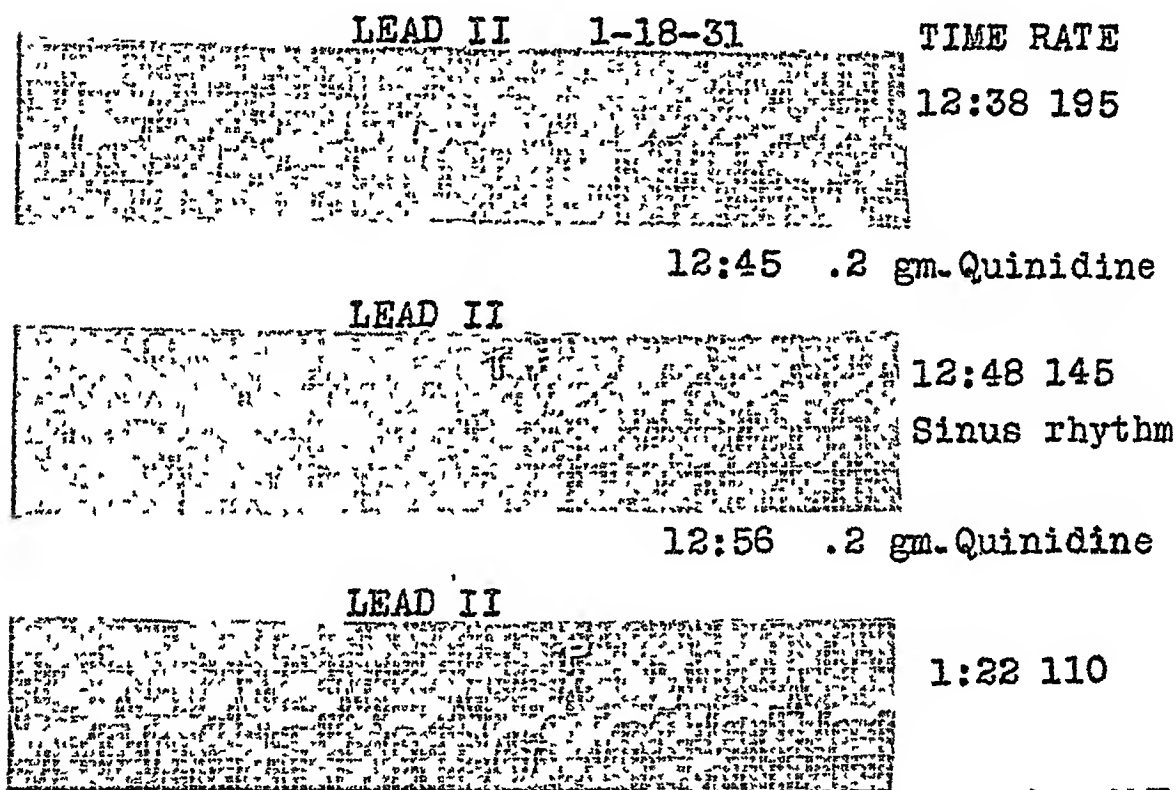


FIG 4 Nodal tachycardia Quinidine sulphate Tracings three to seven minutes, string constantly observed

no intermission, though previously it had (See table I)

The next day with a rate of 170 a total of 16 cc of digifolm was given by vein in divided doses during a period of thirty-four minutes. Slowing of the rate began early, and in thirty-six minutes sinus mechanism ensued with the fairly slow rate of 95. The change in rate was so gradual that it was impossible to tell from movement of the string when the change of mechanism took place, though the patient knew when it occurred by the relief of palpitation. (See figure 6)

back to an auricular rhythm which persisted until the next day, when he had a slow sinus rhythm. There can be no doubt but that he had enough atropine to block the vagus and digitalis enough to cause full effect. (See figure 7)

COMMENT

In two of the above three cases in which quinidine was used there was an arrest of the attack. In both the mechanism was possibly nodal. In all three there was a definite slowing of

TABLE I

The effect of administering quinidine sulphate in Case IV

E C G	TIME	MEDICATION	HEART RATE	REMARKS
1	7 48 P M 8 00 P M	0.2 grams quinidine intraven	170	
2	8 30 P M 8 35 P M	0.2 grams quinidine intraven	160	
3	8 42 P M 8 52 P M	0.2 grams quinidine intraven	150	
4	8 57 P M 9 16 P M	0.2 grams quinidine intraven	150	
5	9 22 P M		150	
6	9 27 P M		150	Auricular tachycardia persists
7	9 46 P M		150	

LEAD II 1-27-31

TIME RATE

11:50 180

11:54 4 cc. Digalen

LEAD II

12:00 4 cc. Digalen

12:09 155

12:27 4 cc. Digalen

LEAD II

12:42 135

LEAD II

1:00 50
Sinus Brady-
cardia

FIG 5 Nodal tachycardia Digitalis Tracings every five minutes, strmg observed constantly

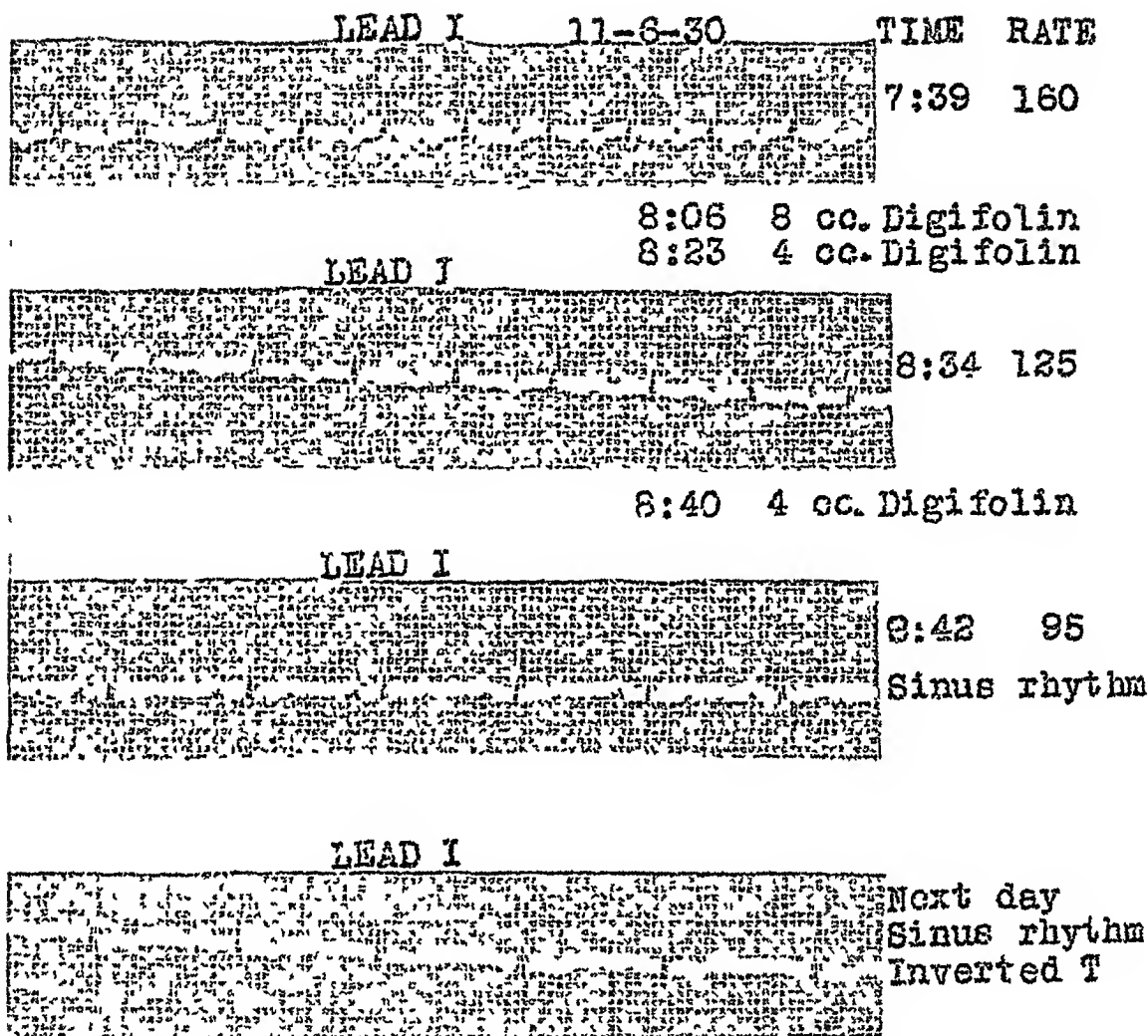


FIG 6 Auricular tachycardia Digitalis Tracings every one to six minutes

the rate of the attack. In the two in which the attack was arrested, the sinus rate was at first almost as fast as the paroxysmal rate. Assuming that the mechanism of paroxysmal tachycardia is a circus movement, quinidine slows the rate by slowing conduction and arrests the attacks by increasing the refractory period of the auricular muscle. In the two cases reacting to quinidine, in one in which quinidine was inactive, and in one in which quinidine was not used, digitalis slowed the rate and arrested the attack as did quinidine. It is difficult to explain the action of digitalis in slowing the rate

for in other examples of circus movement, namely flutter, it increases the rate. By its effect through the vagus, digitalis may decrease the conduction time out of proportion to the decrease in the refractory period and end circus movement, or it may end circus movement by its effect on the muscle in lengthening the refractory period.

In one case digitalis failed to arrest permanently an attack after complete paralysis of the vagus by atropine. It would seem, therefore, that digitalis arrests the attacks by action on the vagus. With atropine, digitalis slowed the auricular rate.

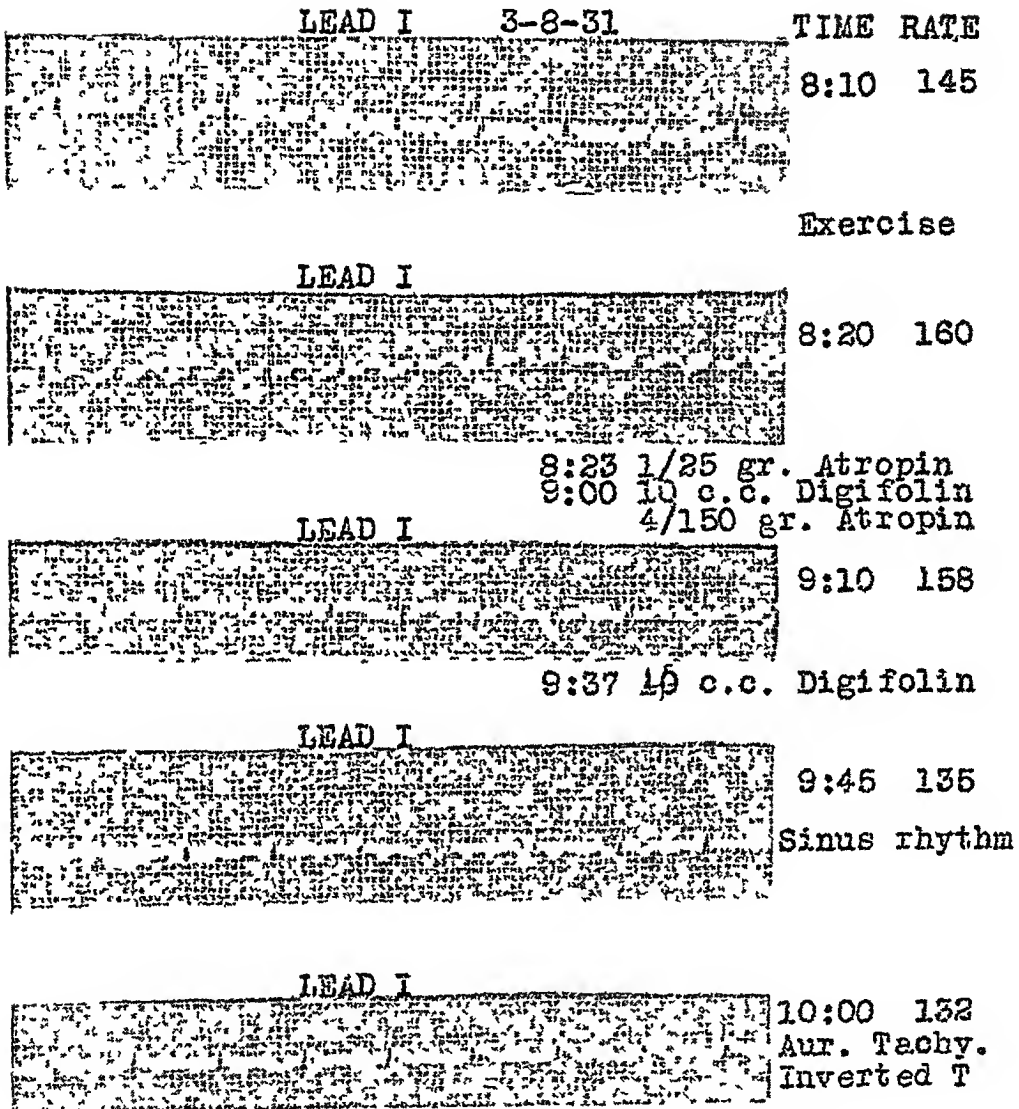


FIG 7 Auricular tachycardia Digitalis after atropine

SUMMARY

The important features in a series of twenty-six cases of supraventricular tachycardia are noted. Cases of unusual duration are reported, one case having an attack lasting three years, another being in a permanent attack for nearly six years unless treated.

Quinidine in most cases of supraventricular tachycardia is the more desir-

able drug for arresting an attack, though in the presence of heart failure digitalis will act and may be the drug of choice. In two cases where quinidine was continued for a year, it had to be used in increasing doses.

Continuous digitalization has been extended over periods as long as one and a half years. While the continuous use of digitalis is to be preferred over

quinidine, the drug must be used in such large doses that toxic effects appear.

Both digitalis and quinidine will slow the rate and arrest the attacks in the same patient. Until the mechanism of these attacks is better known, the mode

of action of drugs cannot be explained.

Digitalis did not arrest an attack in a patient who had received 1/15 grain of atropine.

Both digitalis and quinidine act well by mouth, and few cases need the drugs by vein.

REFERENCES

- ¹LEWIS, T The effects of vagal stimulation upon atrioventricular rhythm, *Heart*, 1914, v, 247
- ²LEWIS, T The experimental production of paroxysmal tachycardia and the effect of ligation of the coronary artery, *Heart*, 1909, i, 28
- ³BOUCHUT, and BARRIER, J Infarctus de la region sino-auriculaire dans un cas de tachycardia, *Lyon méd*, 1924, CXXXIII, 444-446
- ⁴BOORMAN, MILTON C, and McMILLAN, THOMAS A Destruction of sino-auricular node in dog's heart by radon, *Am Heart Jr*, 1927, III, 208-219
- ⁵MAJOR, R H, and WAHL, H R Paroxysmal tachycardia with myocardial lesion, *Am Heart Jr*, 1930, v, 477-481
- ⁶ANDERSON, G H Auricular paroxysmal tachycardia, a post-diphtheritic complication *N W Med*, Seattle, 1924, XXIII, 467-469
- ⁷KERN, R A Paroxysmal tachycardia following use of air in testing fallopian tube patency, *Jr Am Med Assoc*, 1925, LXXXVI, 623
- ⁸LUTEN, D Tachycardia as a result of digitalis administration, *Ann Clin Med*, 1924, III, 197-198
- ⁹HOWARD, TASKER Double tachycardia—coexistent auricular and ventricular tachycardia due to digitalis, *Am Jr Med Sc*, 1927, CLXXIII, 165-168
- ¹⁰GALLI, GIOVANNI Attacks of paroxysmal tachycardia following atropine, *Heart*, 1920, IV, III
- ¹¹TERRELL, TRUMAN Personal communication
- ¹²KORNS, H M An experimental and clinical study of quinidine sulphate I Experimental, *Arch Int Med*, 1923, XXXI, 15
- ¹³CARR, JAMES G Paroxysmal tachycardia, *Ill Med Jr*, 1927, LI, 123-127
- ¹⁴THOMAS, W A, and POST, W E Paroxysmal tachycardia in migraine, *Jr Am Med Assoc*, 1925, LXXXIV, 589
- ¹⁵COLGATE, C E, and McCULLOCH, HUGH Paroxysmal tachycardia in infancy, *Am Heart Jr*, 1926, II, 160-165
- ¹⁶LEWIS, T Paroxysmal tachycardia, the result of ectopic impulse formation, *Heart*, 1909, i, 262
- ¹⁷CRAWFORD, J HAMILTON Supraventricular paroxysmal tachycardia with a varying site of stimulus origin, *Am Heart Jr*, 1928, III, 319-327
- ¹⁸OTTO, H L and GOLD, HARRY Auricular paroxysmal tachycardia Effect of epinephrine, quinidine, atropine and quinine, *Am Heart Jr*, 1926, II, 1-12
- ¹⁹WILLIUS, FREDERICK A Paroxysmal acceleration of the heart rate, *Am Heart Jr*, 1927, III, 230
- ²⁰BARNES, A R and WILLIUS, F A Cardiac pain in paroxysmal tachycardia, *Am Heart Jr*, 1927, II, 490
- ²¹BARNES, A R Cerebral manifestation of paroxysmal tachycardia, *Am Jr Med Sci*, 1926, CLXXI, 489
- ²²GILBERT, MAURICE A case of paroxysmal tachycardia treated and cured by quinidine sulphate, *Schweiz med Wchnschr*, 1925, LV, 1207-1209
- ²³GALLI, G Final contribution to the mechanism of arrest and onset of the attacks of paroxysmal tachycardia, *Gazz d ospedali*, 1923, XLIV, 533-535
- ²⁴FELL, H S, and GILDER, M D D The regularity of simple paroxysmal tachycardia, *Heart*, 1921, VIII, 1
- ²⁵FIESSINGER, C Cure of paroxysmal tachycardia, *Bull Acad de méd*, Paris, 1919, LXXXI, 478

- ²⁶Worrie, Jos B, and Bellet, Samuel
Cessation of attacks of auricular paroxysmal tachycardia by use of calcium, *Ann Int Med*, 1931, iv, 795-804
- ²⁷Stippe, Waud, and Schliephake, E
Cholin in paroxysmal tachycardia, *Munch, med Wchnschr*, 1925, LXXII, 1997-1999
- ²⁸Wilson, F N, and Wishart, S W
The effect of the intravenous administration of digitalis in paroxysmal tachycardia of supraventricular origin, *Am Heart Jr*, 1930, v, 549
- ²⁹Eakin, W W Paroxysmal tachycardia, *Canadian Med Assoc Jr*, 1926, LXI, 1654-1661
- ³⁰Boden, E, and Neukirch, P *Deutsch Arch f klin Med*, 1921, CXXXVI, 181-190
- ³¹Iliescu, C C, and Sebastiani, A Notes on the effect of quinidine upon paroxysms of tachycardia, *Heart*, 1923, 1, 223
- ³²Sprague, H B, and White, P D Cases illustrating indications for use of quinidine sulphate in heart disorders *Boston Med and Surg Jr*, 1925, CXCII, 91-100

Answer "Yes" or "No"

"NATURALLY, from the very nature of its objective, the hypothetical question must be a biased and one-sided affair in order to be of value as a piece of evidence carrying weight with those deciding the case. It is just this one-sidedness which frequently taxes the physician-witness's conscience in fairly answering by the generally requested 'yes' or 'no'. No medical expert can be compelled to answer either positively or negatively a hypothetical question that is based either wholly or in part upon subject matter so arranged that he cannot conscientiously give the reply asked for. Furthermore, a medical expert's answer to the effect that he does not know, is also expressing an opinion, and is considered a reasonable and logical reply thereto. The lawyer, to be sure, usually requests hypothetical questions to be answered in the affirmative or negative by monosyllables, *but it nevertheless remains the inalienable right of the witness to testify according to the dictates of his conscience in harmony with his oath as a witness, and not at all according to the preconceived notions of a lawyer propounding a debatable question*"

(From *Medical Jurisprudence* by CARL SCHEFFEL, J Blakiston's Son and Company, Philadelphia, 1931)

The Response of the Cardiovascular System to Respiratory Strain: A Measure of Myocardial Efficiency*

BY ALLAN EUSTIS, B S , M D , F A C P , *New Orleans, La*

THE importance of determining the functional capacity of the myocardium in organic heart disease has engaged the attention of cardiologists for many years, but in 1922, Brittingham and White,¹ after a careful study of the tests then in use, concluded that there was no satisfactory test for cardiac function. During this same year Frost² arrived at the same conclusion, and at the annual meeting of the Association of Life Insurance Medical Directors of America, he described a new cardiorespiratory test developed in collaboration with Dwight, which was being used by the New England Life Insurance Company in evaluating cardiac cases. A report of this meeting was not published in the current medical journals which probably accounts for its being overlooked by the profession at large, but subsequent publications by Frost³ should have augmented the scant attention which it has received, especially at the hands of the cardiologists, although Herrmann⁴ in 1927 states, "The cardiorespiratory test as described by Frost is certainly a most

promising clinical method of estimating the functional state of the circulatory system." Several of my publications⁵ bear evidence that its clinical value has been appreciated by me since 1924, and at the Sixth Annual Congress of Anesthetists in Washington in May, 1927, I suggested that a simplification of Frost's original technique, utilizing only steps 6, 7 and 8, would result in a simple test whereby anesthetists could judge the patient's cardiovascular state before an anesthetic was given. Later, I published⁶ a description of the modified technic, which I have been using for the past five years.

In following the progress of cases of chronic myocardial insufficiency the cardiorespiratory test has been of inestimable value to me, while the therapeutic indications have often been predicated upon the patients' response to this test, as well as the diagnosis being suggested by same. Common sense should prevail in the interpretation of the response, as Schmitz⁷ so aptly suggests in a resumé of the value of various heart function tests, when he calls attention to the fact that most investigators have made the error of employing the various tests as heart tests rather than as tests of the person with

*Presented at the Baltimore meeting of the American College of Physicians, March 20, 1933.

heart disease. The cardiorespiratory test depends upon the physiological fact, that increase in intrathoracic pressure caused by forcible expiration, results in a rise in systolic blood pressure, a subsequent fall, and then a rise above that of the initial systolic blood pressure in an individual with a normal cardiovascular system.

A study of 160 responses on 125 cases taken from my office files, forms the basis of this paper, no attempt being made to review other cardiac functional tests. However, attention should be given to a recent combination test devised by Mackenzie⁸ and his co-workers in the Medical Department of the Prudential Life Insurance Company, which is called the flarimeter test, this being an ingenious combination of the step test, cardiorespiratory test, and the ability to hold the breath after exercise. I have had but little personal experience with this test, but it appears too complicated for general clinical use. Yet, the spirometer used in the test for expiration is probably preferable to the simplex spirometer, which as an accurate measure of vital capacity, is admittedly open to criticism.

A letter recently received from Frost, who is Medical Director of the New England Mutual Life Insurance Company, where the cardiorespiratory test has been in use in his department since 1922, will bear quoting in full. He writes:

"We are still using the cardiorespiratory test routinely in our work and think as much of it as ever. Our experience is now based on from 8,000 to 10,000 such tests. We have just finished investigating 5,000 individuals whom we have accepted upon the basis of the test and are satisfied that it provides us with the means of controlling

the mortality in the circulatory cases at least for a period of eight years, which is, of course, the period of our present study. We still believe that it gives us an idea of the ability of the circulation at the time of examination which we can obtain in no other way. You may be interested to know that in the 5,000 cases which we have just investigated, the gross mortality of the group was 42 per cent of the American Experience Table. Analyzing this material more carefully, we find that in all the cases in which the reaction of the test has been a straight normal we have a mortality of 30 per cent. On the other hand, in those cases in which the reaction tended to abnormality, in particular, of the hyperactive type, the mortality mounts to 75 per cent. In other words, with an average mortality of 42 per cent, in the presence of a perfectly straightforward, normal cardiorespiratory test, we have a mortality of 30 per cent and in the presence of the tests bordering upon abnormality we have the higher mortality of 75 per cent. From our point of view, therefore, basing our results on mortality figures, our experience has been entirely satisfactory and so far as we know better than any hitherto obtained."

The modified technic of the cardiorespiratory test which I have adopted and used extensively for the past five years is as follows. After physical examination of the patient and recording of results, the systolic and diastolic pressure is taken by the auscultatory method with the patient seated, the pulse rate being counted at the same time by auscultation over the brachial artery. The pressure in the cuff is then released and the patient told to expire through the spirometer after full inspiration, cautioning him to watch the pressure gauge and keep the pressure uniform at 20 mm of mercury. The systolic pressure is taken before the patient inhales, and after expiration has been completed, the maximum systolic pressure being recorded. With-

PROTOCOL OF CASES

No	Date	Age	Diagnosis	Pulse		Blood Pressure		Response	Base Line	Cap'ty Blown	Comment
				Before	After	Before	After				
1	3/13/26	51	Chr myocarditis	68	72	118/60	118/70	10-10-15	Stationary	285-370-265	Poor
2	8/25/29	57	Myocarditis, angina pectoris	80	80	125/80	125/80	10-3-10	Falling	100-90-100	Poor
3	10/21/29	40	Myocarditis	80	80	140/85	148/90	10-15-20	Stationary	120-130-120	Fair
4	5/15/30	48	Chr valvular heart disease	72	76	135/90	140/90	30-45-55	Ascending	280-280-270	Good
5	3/31/30	75	Chr myocarditis	68	74	160/90	164/90	10-15-10	Stationary	140-160-160	Poor
6	10/9/29	52	Myocardial insufficiency	84	84	135/90	135/90	15-20-25	Ascending	200-200-200	Fair
7	10/21/28	43	Diabetes mellitus, myocard insuff	80	96	120/80	120/80	10-15-18	Stationary	160-160-170	Poor
8	5/20/30	56	Carcinoma of duodenum	120	136	145/100	160/100	30-40-40	Ascending	200-210-200	Good
9	5/28/31	49	Chronic valvular heart disease	84	90	116/76	120/80	24-36-44	Ascending	180-180-190	Good
10	2/2/30	58	Chr myocarditis	76	84	135/90	135/90	15-25-35	Ascending	160-160-160	Good
11	4/1/30	59	Fibroid the lungs, duodenal ulcer	76	84	105/70	105/70	10-15-15	Stationary	160-170-180	Fair
12	3/26/30	32	Chr myocarditis, chr tonsillitis	118	124	144/90	144/90	20-40-50	Ascending	160-160-160	Good
13	3/10/30	30	Myocardial insufficiency	76	80	115/80	112/80	10-15-15	Falling	220-240-230	Good
13b	4/22/30	30	Myocardial insufficiency	80	80	110/75	112/70	15-20-30	Ascending	200-200-200	Poor
14	4/16/30	51	Myocardial insufficiency	60	68	110/70	110/70	0-4-2	Stationary	160-180-160	Poor
15	8/10/29	47	Myocardial insufficiency	80	80	125/80	118/80	15-10-10	Falling	200-200-210	Poor
16	1/27/30	47	Chr cholecystitis, myocarditis	84	84	120/80	122/80	10-20-30	Ascending	220-240-230	Fair
17	3/24/30	55	Myocardial insufficiency, cholelithiasis	76	76	116/90	120/90	14-20-20	Ascending	170-200-200	Fair
18	8/28/29	18	Chr valvular heart disease	120	120	120/80	120/80	20-25-30	Stationary	180-180-180	Good
19	10/1/29	58	Hypertension	64	64	170/90	160/90	15-25-35	Ascending	180-180-180	Good
20	12/1/28	47	Myocardial insufficiency	96	104	135/90	120/90	5-5-10	Falling	180-190-200	Poor
21	3/16/28	52	Myocarditis, dilatation	78	84	150/140	140/130	10-15-10	Stationary	60-70-65	Poor
21b	1/23/28	52	Myocarditis, dilatation	88	88	124/80	128/80	6-6-6	Stationary	80-80-80	Poor
21c	6/7/28	52	Myocarditis, dilatation	84	84	135/80	135/80	10-15-20	Ascending	60-60-65	Fair
22	4/2/29	52	Myocardial insufficiency	68	68	120/80	120/80	6-10-15	Stationary	180-160-160	Poor
23	10/3/28	52	Cardio renal disease	84	90	165/90	170/90	15-5-15	Ascending	100-120-100	Poor
24	4/9/29	60	Myocarditis, dilatation	68	68	140/80	140/80	10-15-20	Ascending	150-150-150	Fair
25	8/4/28	18	Myocarditis, sinus arrhythmia	76	80	120/80	140/80	25-40-40	Ascending	200-200-200	Good
25b	9/4/28	18	Myocarditis, sinus arrhythmia	80	84	110/70	120/80	25-30-30	Ascending	185-215-215	Good
26	9/15/28	48	Infectious arthritis	80	80	108/60	98/60	20-10-20	Stationary	150-160-160	Poor
27	1/9/29	21	Neuro circulatory asthenia	80	80	108/70	110/70	7-7-10	Stationary	120-110-115	Poor
28	1/28/28	67	Cardio-renal disease, diabetes mellitus	76	80	145/100	145/100	10-15-25	Stationary	120-120-120	Fair
28b	12/24/30	67	Cardio renal disease, diabetes mellitus	76	76	150/90	155/90	15-20-20	Stationary	180-180-140	Fair
29	6/8/28	23	Chronic myocarditis, dilatation	84	68	108/80	100/80	7-3-10	Falling	30-30-35	Poor
30	8/3/27	58	Chronic myocarditis	80	84	120/80	120/80	40-30-10	Stationary	310-310-310	Poor
31	12/3/26	38	Chr cholecystitis, chr arthritis	80	68	112/80	120/90	16-4-6	Ascending	140-150-160	Poor
32	4/11/27	58	Obesity, chr prostatitis	68	68	113/70	172/70	20-30-35	Ascending	225-210-210	Good
32b	8/2/28	50	Obesity, chr prostatitis	80	84	130/80	135/80	15-20-30	Ascending	120-140-130	Good
33	2/18/27	43	Chronic myocarditis	84	84	85/60	85/60	25-25-25	Ascending	240-240-225	Fair
34	6/20/24	55	Chronic cholecystitis	80	80	130/80	130/80	0-0-20	Stationary	275-270-270	Poor
35	2/1/28	9	Chr valvular heart disease	108	96	95/45	90/40	20-28-28	Stationary	80-90-90	Fair
36	7/21/26	20	Chr myocarditis								
37	5/4/27	44	Post-influenzal myocarditis	80	88	112/70	108/70	22-10-2	Descending	90-100-100	Poor
38	5/29/28	60	Mediastinal adenitis	88	84	110/60	116/70	14-25-30	Ascending	195-190-195	Good
39	9/10/27	25	Neurasthenia	76	76	130/80	138/80	25-30-40	Ascending	160-170-180	Good
40	11/6/29	36	Hypotension, pregnancy	76	76	105/80	105/80	10-15-20	Stationary	225-225-225	Fair
41	3/13/28	56	Chronic nicotine poisoning	84	88	135/90	140/90	15-25-35	Ascending	220-230-230	Good
42	3/19/26	42	Chronic myocarditis	72	72	142/100	130/90	2-2-4	Falling	160-160-180	Poor
42b	3/19/26	42	Chronic myocarditis	100	84	150/100	170/100	20-30-50	Ascending	180-180-180	Good
43	2/18/27	43	Chronic cholecystitis	72	80	140/90	150/90	10-20-40	Ascending	130-120-180	Good
43b	4/19/26	47	Cardio renal disease, hypertension	100	120	220/140	220/130	20-30-30	Ascending	170-170-170	Fair
44	11/18/27	53	Chr interstitial nephritis	65	60	185/120	190/130	15-25-55	Ascending	160-140-180	Good
45	5/2/23	58	Hypertension	80	80	100/60	100/60	10-20-30	Ascending	200-220-220	Good

46	3/4/27	64	Carcinoma of lungs	72	80	110/100	110/70	18-20-30	Ascending	150 160 135	Fair
47	10/12/20	56	Chronic myocarditis	106	95	118/70	120/110	20-20-20	Ascending	240 240 230	Fair
48	5/12/28	60	Chronic myocarditis	84	84	160/80	170/80	20-25-20	Stationary	210 210 215	Fair
49	5/5/27	47	Cirrhosis liver, chr myocarditis	112	80	88/50	88/60	2-8-8	Falling	105 105 00	Poor
50	6/19/24	50	Fibrosis of lungs	80	80	160/00	160/00	10-20-30	Stationary	200 300 315	Good
51	7/26/27	71	Chronic myocarditis	72	72	110/00	105/00	10-5-5	Falling	195 100 180	Poor
52	12/15/25	55	Chronic aortitis	64	72	128/80	140/80	15-28-30	Ascending	315 315 315	Fair
53	12/16/27	62	Chr myocarditis, hypertension	80	80	100/80	140/80	5-0-0	Falling	120 140 140	Poor
54	4/1/20	41	Chronic cholecystitis, chr myocarditis	04	72	128/80	140/80	20-20-30	Ascending	300 300 300	Good
55	11/25/25	52	Hypotension	88	88	92/60	08/70	24-18-20	Stationary	300 315 315	Fair
56	5/5/27	58	Hypothyroidism	76	76	98/00	100/00	10-20-35	Ascending	00 105 105	Good
57	12/3/27	66	Chronic prostatitis, myocarditis	76	76	210/80	200/00	20-10-10	Stationary	110 130 120	Poor
58	7/11/27	43	Chronic cholecystitis and appendicitis	76	70	130/80	128/80	20-40-00	Ascending	300 300 315	Good
59	4/2/27	42	Hyperchloridia	78	78	128/80	128/80	20-20-20	Stationary	168 190 200	Fair
60	8/4/26	57	Post influenza myocarditis	64	68	138/80	140/80	0-0-20	Falling	255 255 255	Poor
61	5/29/28	44	Obesity	76	76	135/90	135/90	15-20-35	Ascending	200 200 200	Good
62	2/26/27	47	Routine physical examination	72	72	130/80	135/80	30-40-50	Ascending	285 285 285	Good
63	9/5/27	32	Infectious arthritis	76	84	108/70	110/70	10-16-20	Ascending	100 160 100	Fair
64	9/6/27	56	Chr cholecystitis, chr myocarditis	76	76	106/00	108/00	20-30-35	Ascending	105 165 105	Good
65	2/15/28	30	Paroxysmal tachycardia	78	80	110/00	110/80	10-20-30	Ascending	210 210 240	Good
66	4/18/27	77	Dilatation of heart, chr myocarditis	80	80	195/110	180/100	10-10-10	Stationary	150 105 165	Poor
67	11/30/27	75	Cardio renal disease, dilatation of heart	76	80	210/100	160/80	-10-30-70*	Falling	120 100 100	Poor
68	2/25/27	58	Partial heart block	76	80	132/80	135/80	18-8-28	Ascending	180 190 190	Fair
69	11/14/27	40	Hypertension, chronic myocarditis	76	84	180/150	190/140	20-30-20	Stationary	180 180 160	Fair
70	1/15/20	49	Chronic myocarditis	84	84	135/90	135/90	15-26-35	Stationary	95 100 100	Good
71	2/4/29	30	Chr valv heart disease, card dilat	76	76	130/75	130/80	5-0-0	Falling	180 180 180	Good
72	9/5/28	58	Chr cholecystitis, chronic myocarditis	84	84	150/80	135/80	0-10-20	Falling	210 110 100	Poor
73	7/19/27	53	Chronic valvular heart disease	76	76	145/90	148/100	15-25-45	Ascending	120 250 250	Good
74	3/18/29	55	Chronic valvular heart disease	98	84	170/100	170/100	25-30-40	Ascending	180 180 175	Good
75	8/17/28	46	Chronic myocarditis, dilatation of heart	104	104	190/140	185/170	20-30-0	Falling	140 140 140	Poor
76	9/30/25	34	Abscess of lungs, dilatation of heart	76	76	85/40	80/40	15-25-15	Stationary	180 180 195	Poor
77	5/29/28	50	Acute glomerulo nephritis, hypertension	68	80	154/100	100/100	10-20-30	Ascending	170 180 100	Good
77b	8/1/28	50	Chronic myocarditis	68	76	150/100	150/100	20-25-30	Ascending	120 130 120	Fair
78	4/2/29	17	Dilatation of heart	76	80	170/90	170/90	10-20-25	Stationary	120 130 120	Poor
79	2/8/29	29	Neuro circulatory asthenia	112	124	108/80	118/80	20-30-40	Ascending	80 80 80	Good
80	4/17/28	43	Chr myocarditis, mediastinal adenitis	92	92	108/80	108/70	2-2-2	Stationary	100 100 190	Poor
81	3/18/30	00	Hypertension	100	96	145/95	145/90	25-30-35	Ascending	180 180 160	Good
82	8/22/28	40	Dilatation of heart	88	84	135/80	130/80	20-20-25	Stationary	140 150 150	Fair
83	2/4/29	30	Paroxysmal tachycardia	64	84	100/120	170/120	20-30-40	Ascending	180 180 180	Good
84	4/6/20	51	Chronic cholecystitis	94	100	118/110	108/80	8-8-10	Falling	150 160 150	Poor
85	3/5/20	61	Chr myocarditis, chr cholecystitis	72	72	176/120	180/120	20-30-45	Ascending	110 100 120	Good
86	8/27/30	40	One year after cholecystectomy	84	84	170/120	170/110	20-30-48	Stationary	130 140 130	Good
87	11/14/28	64	Myocardial insufficiency	48	76	100/60	120/80	22-35-38	Ascending	100 160 160	Good
88	11/7/27	51	Myocarditis hypertension	68	62	130/80	120/80	10-5-5	Falling	170 175 180	Poor
89	2/2/20	50	Neuro circulatory asthenia	76	76	160/100	150/100	10-0-0	Falling	80 90 75	Poor
90	5/10/27	38	Myocardial insufficiency	68	76	118/70	134/80	10-15-20	Ascending	285 285 270	Fair
90b	0/2/27	38	Myocarditis, compensation	96	96	130/80	130/80	10-30-20	Stationary	225 240 195	Fair
90c	3/1/31	42	Physical examination	88	80	125/80	128/80	30-40-45	Ascending	270 285 285	Good
91	1/11/27	39	Myocardial insufficiency	84	88	126/80	128/80	15-25-35	Ascending	180 180 180	Good
91b	3/2/27	30	Myocardial insufficiency	76	76	118/70	104/70	30-30-20	Stationary	255 255 255	Fair
91c	4/3/27	30	Myocardial insufficiency	76	76	128/80	118/70	12-22-2	Falling	285 295 285	Poor
91d	10/1/27	30	Myocardial insufficiency	72	72	115/70	110/70	20-18-10	Stationary	240 270 260	Poor
91e	12/5/27	39	Myocardial insufficiency	76	76	130/80	138/80	6-10-0	Falling	300 210 210	Poor
91f	19/5/27	39	Myocardial insufficiency	68	70	118/70	118/70	10-20-25	Ascending	180 180 200	Fair
91g	2/10/31	43	Myocardial insufficiency	76	70	138/90	135/90	10-15-20	Ascending	220 240 245	Fair

PROTOCOL OF CASES—Continued

No	Date	Age	Diagnosis	Pulse		Blood Pressure		Response	Base Line	Cap'ty Blown	Comment
				Before	After	Before	After				
92	11/20/28	61	Myocarditis, hypertension	68	76	170/110	150/90	10-10-10	Stationary	140-140-140	Poor
92b	5/19/30	62	Myocarditis, hypertension	70	76	170/100	170/100	30-40-45	Ascending	160 160-160	Good
92c	2/26/31	63	Myocarditis, hypertension	76	76	165/100	175/100	20-35-45	Ascending	140-140-140	Good
93	11/27/25	55	Adhesive pericarditis, myocarditis	120	112	118/80	110/80	12-12-0	Stationary	180 180-180	Poor
93b	2/4/26	56	Adhesive pericarditis, myocarditis	112	92	118/80	124/80	10-20-25	Ascending	165-165-165	Fair
93c	2/28/31	61	Adhesive pericarditis, myocarditis	104	112	120/90	120/90	18-15-18	Stationary	80- 90-100	Poor
94	1/20/28	58	Myocarditis, angina pectoris	80	120	140/90	140/90	20-30-20	Ascending	160-180-180	Fair
95	11/30/27	48	Myocarditis, angina pectoris	72	76	108/60	104/60	40-30-20	Stationary	220-220-220	Fair
96	11/3/26	57	Hypertension	84	90	225/125	215/125	10-30-40	Stationary	240-240-240	Good
97	9/28/28	48	Hypertension	88	88	210/150	215/160	30-35-40	Ascending	230 240-250	Good
98	2/6/26	53	Hypertension, hypertrophy of heart	84	96	190/140	215/160	5- 5-10	Stationary	215-225-230	Poor
99	3/17/26	46	Hypertension, pyonephritis	100	100	170/120	170/120	20-20-40	Stationary	270-275-285	Fair
99b	9/26/28	48	Hypertension, decompensation	80	84	170/110	165/110	10-15-20	Stationary	200-190-190	Good
99c	3/6/31	51	Hypertension, compensation	64	68	190/120	220/130	30-50-	Ascending	160-160-	Good
100	4/5/29	51	Hysteria	88	84	174/110	194/110	12-26-46	Ascending	140-160 160	Good
101	6/3/27	48	Asthma	76	76	110/60	120/60	20-30-40	Ascending	225-240-240	Good
102	12/15/24	38	Neurasthenia	76	92	130/90	136/90	40-40-60	Ascending	155-165-180	Good
103	5/6/25	34	Neurasthenia	90	100	118/70	120/70	10-14-20	Ascending	105-165-180	Fair
104	4/23/29	50	Chronic cholecystitis	80	88	140/90	140/90	10-14-20	Stationary	100- 80- 80	Poor
105	1/23/28	74	Myocarditis, dilatation of heart	64	84	130/80	120/100	10-10-10	Ascending	120-135-120	Fair
105b	2/25/28	74	Myocarditis, dilatation of heart	76	80	118/70	118/70	10-15-20	Stationary	160-160-160	Good
105c	5/3/28	74	Myocarditis, dilatation of heart	74	80	120/80	125/80	14-22-30	Ascending	345-345-345	Good
106	3/1/29	27	Secondary anemia	108	104	118/70	118/70	5-10-0	Falling	225-225-225	Poor
107	10/20/25	50	Myocarditis, hypertension	92	112	160/80	165/90	10-50-60	Ascending	160-180-190	Fair
107b	6/26/27	52	Myocarditis, hypertension	92	96	145/90	142/90	10-50-60	Ascending	60- 60- 60	Poor
108	6/30/27	53	Chronic valvular heart disease	76	76	150/90	145/90	10-20-30	Falling	225-255-255	Poor
109	1/10/30	41	Myocarditis, dilatation of heart	84	88	145/90	145/90	10-20-30	Ascending	270-270-255	Good
110	5/2/30	56	Myocarditis, mediastinal adenitis	96	96	118/70	115/70	10-20-30	Stationary	220 190-210	Poor
111	7/3/21	43	Chronic valv heart disease, myocard	76	74	100/80	100/80	10-20-30	Ascending	180 180-200	Fair
112	8/29/25	38	Chronic cholecystitis	72	72	120/80	120/80	10-20-30	Ascending	180 180-180	Poor
113	1/7/40	58	Myocardial disease	68	68	165/90	165/90	5-5-10	Stationary	140-160-155	Good
114	10/9/28	44	Myocardial disease	76	64	118/80	130/80	15-20-25	Ascending	215-215-215	Fair
115	1/19/31	40	Adherent pericarditis	80	64	115/110	115/110	15-15-15	Stationary	200-200-200	Good
116	12/12/30	57	Angina pectoris, chronic appendicitis	84	92	145/70	150/70	20-35-45	Stationary	180 180-200	Fair
117	7/28/25	55	Chronic myocarditis	80	100	110/70	110/70	10-30-5	Stationary	140-160-155	Good
117b	12/4/28	58	Chronic myocarditis	72	72	130/80	125/80	10-15-20	Ascending	90-100-120	Poor
117c	2/27/31	61	Chronic myocarditis	76	76	128/80	135/80	25-35-40	Ascending	215-215-215	Fair
118	3/2/21	51	Myocarditis, dilatation of heart	76	100	150/90	155/90	5-10-10	Ascending	200-200-200	Good
118b	6/30/27	57	Myocarditis compensation	56	60	135/120	140/90	25-50-40	Stationary	195-210-225	Good
118c	2/20/31	61	Myocarditis, dilatation of heart	64	64	143/100	165/100	20-30-35	Ascending	180-180-195	Good
119	2/21/29	55	Myocarditis, dilatation of heart	84	84	120/70	115/70	5-0-0	Falling	180-180-180	Poor
119b	2/25/31	57	Myocarditis compensation	80	80	130/80	135/80	15-20-35	Ascending	180 200-200	Good
120	2/24/26	62	Myocarditis, dilatation of heart	88	88	110/70	106/70	10-20-20	Ascending	195-195-195	Fair
120b	3/31/27	63	Myocarditis compensation	80	80	130/80	135/80	15-30-40	Ascending	285-285-285	Good
121	7/18/25	48	Paresis of left diaphragm	84	84	130/80	134/80	10-20-30	Ascending	175-175-175	Good
122	1/6/27	62	Myocarditis, compensated	76	76	145/90	145/90	15-25-35	Ascending	120-120-118	Poor
122b	1/3/28	63	Myocarditis, dilatation	120	130	120/75	130/80	10-10-5	Stationary	180 180-195	Good
123	3/9/25	60	Routine physical examination	64	64	110/80	116/80	10-20-30	Ascending	240-210-225	Good
123b	5/5/27	62	Myocarditis, dilatation of heart	76	72	100/65	90/60	10-10-8	Falling	160 140-160	Poor
124	5/13/29	54	Neuro circulatory asthenia	72	64	100/65	132/90	14-24-30	Ascending	180-160-150	Poor
125	12/21/25	31	Chronic nicotine poisoning	80	84	135/90	132/90	14-24-30	Ascending	225 220-240	Good

*Negative response

out releasing pressure in the cuff, the needle of the spirometer is turned to zero, the systolic pressure is again taken and the patient again instructed to inhale fully and expire through the spirometer as before. Three successive readings are then made, corresponding to steps 6, 7 and 8 in Frost's technic. If it is evident that the patient has not expired his full vital capacity, a second test should be made after cautioning him to inhale and expire fully, or, perhaps only a fourth expiration may be necessary.

The results may be plotted as a curve, the change in millimeters of mercury in blood pressure obtained after each expiration representing the response, and the change in millimeters in the blood pressure obtained just prior to each inspiration representing the base line. A normal response should result in an increase of systolic blood pressure after the third expiration of from 30 to 40 mm. A failure to respond, in my experience, denotes a weakened heart muscle. A falling base line is invariably associated with great dilatation of the heart. The test should not be tried on any individual with marked dilatation of the heart, as I have seen in my early experience a near approach to syncope result in such instances, while in others marked cardiac distress has been observed. The test should be used with caution, also, on patients with a history of anginal attacks, as well as on cases of arterial hypertension. These precautions are needful with any other cardiac function test, but, I believe the danger from the cardiorespiratory test is less than with most cardiac tests involving a strain on the heart muscle.

The test is especially valuable in the study of chronic myocardial insufficiency, and in the protocol, where the diagnosis of myocarditis is recorded, it must be interpreted as the commonly used term to express myocardial degeneration, in which there is usually evidence of myocardial insufficiency. In numerous instances, however, the electrocardiographic tracings denoted myocardial disease, while both clinically and by the cardiorespiratory test, the heart muscle was able to function normally. An examination of the protocol will at once be convincing that the test has been of considerable value to me in clinical evaluation of cases, and a discussion of interesting phases of some cases is in order.

DISCUSSION OF PROTOCOL

A study of the protocol shows that of the 160 responses, 56, or 35 per cent, have been listed as poor, i.e., responses below 20 mm, 40, or 25 per cent, as fair, i.e., 20 to 30 mm, and 64, or 40 per cent, as normal, i.e., above 30 mm. These correspond to the interpretations of Frost as, below normal, low normal, and normal respectively. Further examination will also reveal the fact that some responses were recorded as normal, which on strict interpretation should have been classified as hyperactive, the reason for this being, that I have been particularly interested in detecting weakened heart muscles, rather than evaluating the cases from an insurance standpoint. Of the 56 poor responses, only five, or 21 per cent of the total (numbers 22, 26, 34, 87 and 124) failed to exhibit other evidences of a weakened heart muscle after the test. The condi-

tions present in cases numbers 22, 26 and 34 are those often associated with myocardial changes; while no 87 was the response of a man 64 years of age, at which time of life a weakened heart muscle is by no means rare. So it is not illogical to suppose that in these cases the poor response was due to weakness of the heart muscle rather than to vasomotor phenomena. No 124 was obtained on an asthenic individual, who is easily fatigued, with no demonstrable evidence of any focal infection, and with no manifestation of myocardial lesion. His skeletal muscles are flabby, and accepting Starling's idea, that the physiology of the heart muscle as regards its ability to contract and perform work is identical with that of the skeletal muscles, it may be assumed that in this instance, also, the myocardium was weak, though no other symptoms of myocardial insufficiency could be elicited.

In all of the other 51 poor responses, the appearance of a murmur at the apex, or the accentuation of a pre-existing murmur, or an increase in pulse rate, cough or dyspnea were detected after strain was put upon the heart by the test. Some cases (numbers 13, 21, 90, 91 and 92) responding poorly at first examination, responded to the test normally after the heart muscles had been toned up by graduated exercise, and other therapeutic measures. This is especially well illustrated by the responses obtained on case 91 (chart II, D, E and F). Fourteen responses only, on cases of hypertension are recorded, the small number being due to the fact that I rarely run a test on an individual with an

mm or over. Such cases tend to respond excessively to the test and the danger of cerebral hemorrhage from hypertension during the test must be constantly borne in mind. Details of a few of these cases will be found in a discussion of chart IV.

DISCUSSION OF CHARTS

Chart I Responses A, B and C (Case 117) A lawyer, 55 years old, first seen in 1925 (A), weight 202½ lbs, height 5 ft 8¼ in at that time, muscles flabby and pendulous abdomen. There was definite clinical evidence of myocardial insufficiency, but with no organic valvular lesion in the heart. The response to the cardiorespiratory test (A) is characteristic of a flabby heart muscle, a long delay occurring before return of the sounds to the ear after each expiration and a drop in the third step as well as in the base line, with an increase in pulse rate. After removal of diseased tonsils by Dr Lynch, and gradually increasing exercise, with a loss of 10 lbs in weight, he had improved symptomatically by 1928, when test (B) was made. While this shows an improvement in the response to the cardiorespiratory test, it is still below normal for a man of his physique. For the past three years he has engaged regularly in golf with progressive improvement physically, his muscles becoming firm with a loss in weight of 14 lbs, while his response (C) to the cardiorespiratory test is normal.

Responses D, E and F (Case 118) A business executive 61 years of age, weight 164½ lbs, height 5 ft. 7 in, has been under my constant observation since 1912. He had acute dilata-

tion in 1916 which was relieved by one month's rest in bed. Efforts since that time have been devoted to toning up the heart muscle, with the result of gradual improvement in subjective symptoms. In 1924 he still had definite signs of cardiac weakness and his response (D) to the cardiorespiratory test was poor with increase of pulse rate after test. In 1927 there was considerable improvement in clinical symptoms, while the response (E) was better. His vital capacity had increased but weakness of the heart muscle is shown by the drop in systolic blood pressure after the third expiration. At present, there is no clinical evidence of

lack of cardiac compensation, he is actively engaged in business and his response (F) to the cardiorespiratory test is normal.

Responses G and H (Case 119)

Manager of numerous outdoor amusement concessions, 55 years old, weight 194 lbs, height 5 ft 9¾ in, first examined in Feb, 1929. At this time on account of dyspnea and cough and other evidence of dilatation, he was kept in bed for one month. Response (G) to cardiorespiratory test made at initial examination, is very poor with a fall in step 3 and a falling base line. At present there is no clinical evidence of cardiac decompensation, while re-

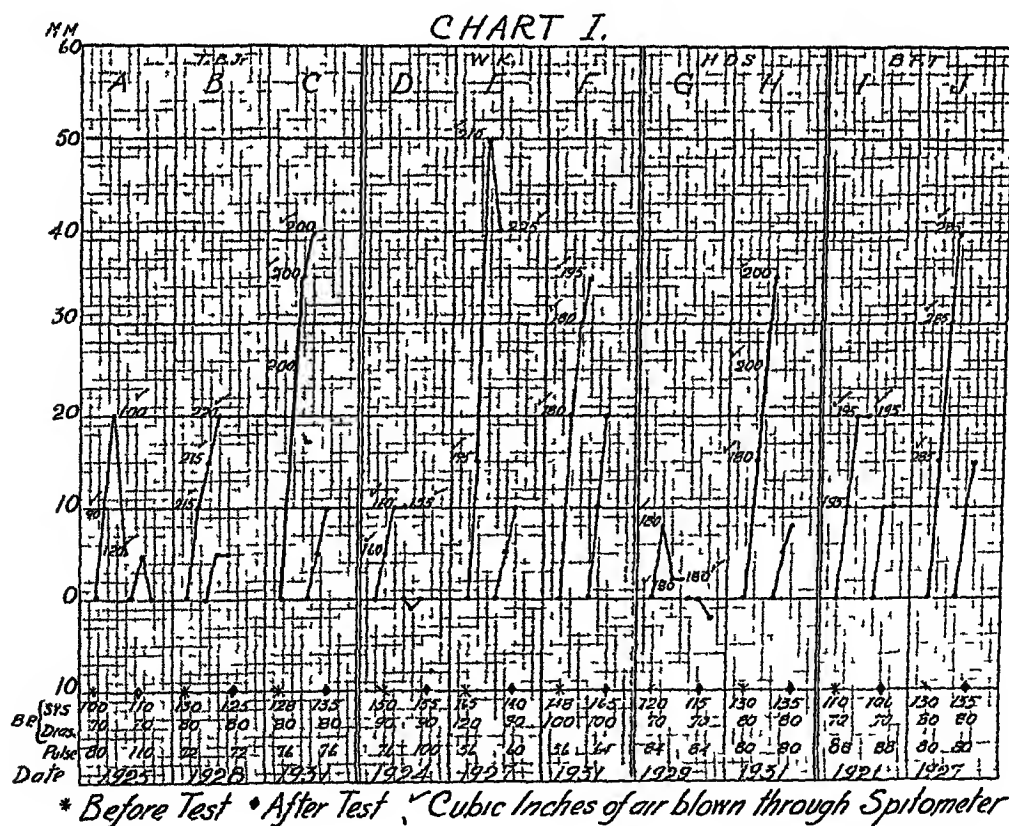
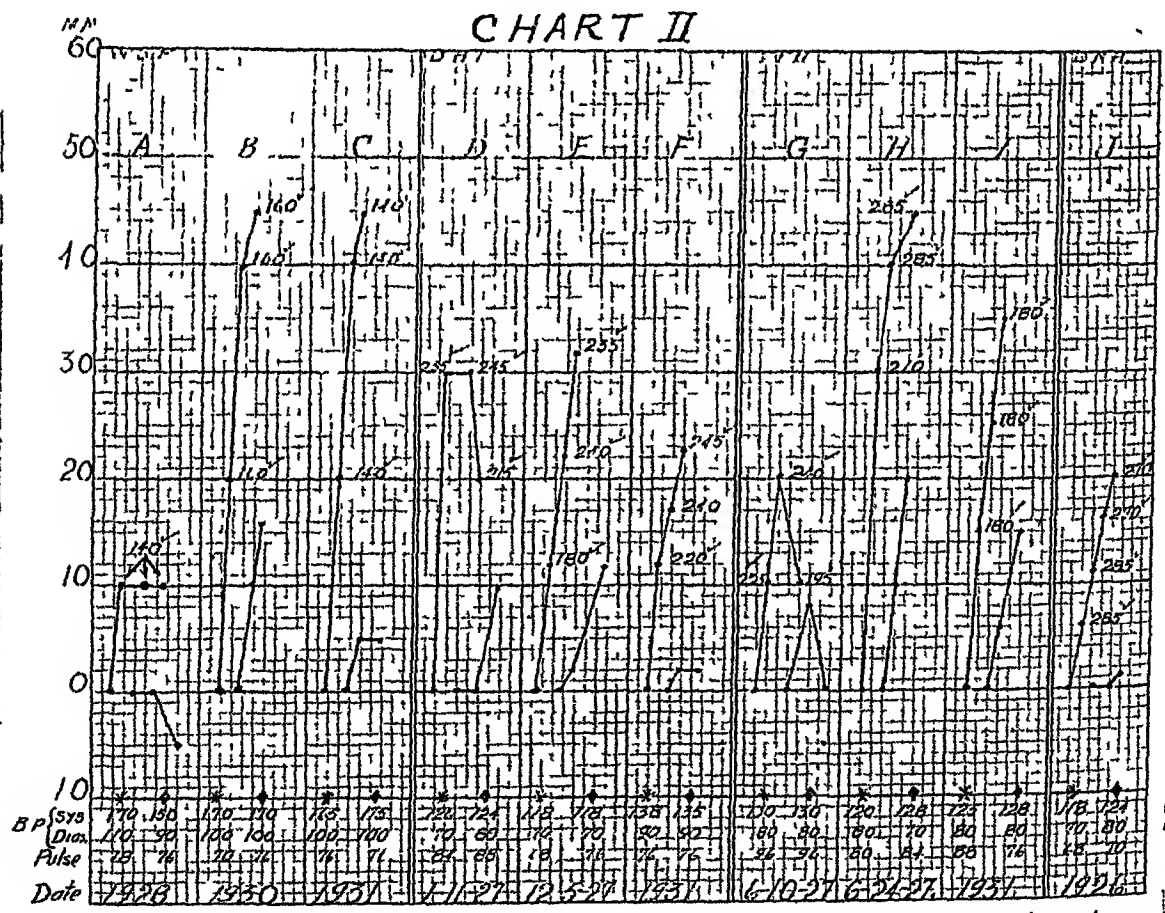


CHART I Showing improvement in responses to the cardiorespiratory test after compensation has taken place. C, F, H, and I are normal responses (see text)

sponse (H) to the cardiorespiratory test is normal

Responses I and J (Case 120) An executive 62 years old, weight 185 lbs ; height 5 ft 8½ in, with clinical evidence of cardiac decompensation following an attack of influenza, gave only a moderate response (I) to the cardiorespiratory test in 1926 After toning up the heart muscle with regular exercise in the form of golf three times a week there was no clinical evidence of cardiac weakness, and his response (J) to the cardiorespiratory test was normal in 1927 He has continued in good health up to the present time

Chart II Responses A, B, and C (Case 92) An executive 61 years old, weight 160¾ lbs , height 5 ft 8½ in, seen first by me, Nov 26, 1928, with an enormously enlarged heart, transverse cardiac dullness measuring 20 cm , extra systoles every third or fourth beat, systolic murmur at apex not transmitted Enlargement of the liver and slight dyspnea on mounting stairs were the only evidences of an impaired heart muscle, but the response (A) to the cardiorespiratory test with a falling base line gave proof of considerable impairment of the heart muscle Clinical improvement was prompt and in 1930 the systolic mur-



* Before Test. ♦ After Test ~ Cubic Inches of air blown through Spirometer.

CHART II Showing varying responses to the cardiorespiratory test Responses B, C, E, H, and I are normal F and J are only fair responses (see text)

mur present at the apex in 1928, had disappeared, the transverse cardiac dullness was 16 cm instead of 20 cm, and the response (B) to the cardiorespiratory test was a high normal one. An examination made in Feb., 1931, showed the heart fully compensated and the response (C) to the cardiorespiratory test was still hyperactive on account of a tendency to hypertension.

Responses D, E, F, and G, H, I represent the type which is often obtained in normal individuals of the obese class, leading sedentary lives, and often showing no symptoms of cardiac decompensation.

Responses D, E, and F (Case 91)

An attorney 42 years of age, has been under my observation since 1918, but had never shown any evidence of cardiac weakness until Jan., 1927. He was obese, weighing 262 lbs., height 5 ft 10½ in. At this time he began to have extra systoles on slight exertion, which were present after test (D). This response is normal in the first two steps but the drop after third step suggested some myocardial weakness. Gradually increasing exercises under a competent physical instructor, with regulation of his diet resulted in a loss of 30 lbs by Dec. 5, 1927. At this time there were no extra systoles, physically he was much improved and the response (E) to the cardiorespiratory test was normal. In 1928 he continued his exercise and his weight varied from 232 to 241 lbs. For the past two years he has given up exercise and his weight has gradually increased to 270 lbs. His response (F) to the cardiorespiratory test is low normal.

Responses G, H, and I (Case 90)

A capitalist 42 years old, weight 167 lbs., height 5 ft 10¾ in., has been under irregular observation since 1915. At college he rowed on the crew but he had taken no regular exercise in recent years. He had "flu" in Dec., 1926. On June 10, 1927 he consulted me for attacks of vertigo, intermittent pulse, and occasional dyspnea. Examination of the heart showed the apex beat 2 cm outside the nipple line, the transverse cardiac dullness was 17 cm., with an occasional, soft systolic blow audible at the apex but not transmitted. The response (G) to the cardiorespiratory test showed the heart muscle responding normally in steps 1 and 2, but falling in step 3. No medication was given, but he was instructed to play golf daily, increasing gradually the number of holes played. On June 24, 1927, two weeks later, he reported free from symptoms. No murmur was audible, heart hypertrophied and response (H) to cardiorespiratory test was normal. One hesitates to report such improvement in cardiac function in so short a space of time as two weeks, but the frequency with which I have seen this unexpected occurrence in patients taking regular exercise, who formerly, were accustomed to sedentary habits, justifies me. If one accepts Starling's teaching, as aforementioned, that the cardiac muscle does not differ functionally from skeletal muscle, this statement is less incredible. The patient reported for examination on March 4, 1931, stating that he had suffered no further recurrence of cardiac symptoms. His response (I) to the cardiorespiratory test was normal, and physi-

cal examination denoted a normal heart

Response J (Case 89) A manager of a retail furniture store, 50 years of age, weight 151¾ lbs, height 5 ft 6 in, leading a very sedentary life, consulted me Feb 2, 1926, complaining of forcible cardiac pulsations at frequent intervals. No dyspnea or other symptoms of cardiac decompensation. The transverse cardiac dullness was 14 cm. There was slight roughening of first sound, but no murmurs. No evidence of cardiac pathology could be detected. Response (J) to cardiorespiratory test is feeble and below normal, but is presented as an example of the type of

response often obtained in an individual leading a sedentary life. Such a patient continues to present a like response until exercise is enforced. I classify this type as a "lazy heart", and the usual response is probably lacking in clinical significance other than from a prophylactic, or life insurance standpoint. This patient is now in excellent health, still works hard and takes no exercise.

Chart III These curves represent three cases which have progressed downward clinically, and two fatal cases.

Responses A and B (Case 93) A physician 61 years old, weight 147 lbs,

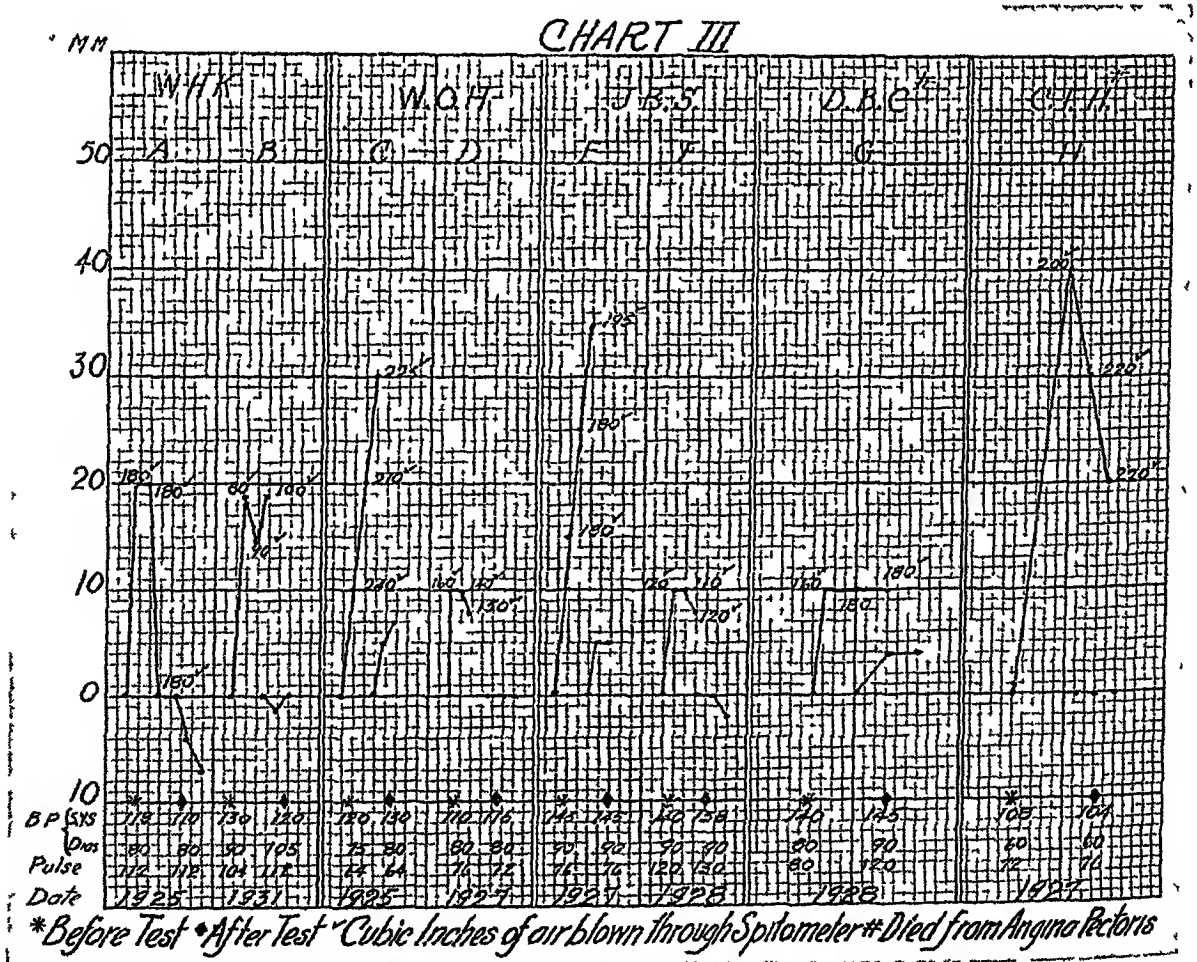


CHART III Showing responses to the cardiorespiratory test on patients who have retrograded clinically. G and H died from coronary thrombosis (see text)

height 5 ft 9 in, has been under my observation since 1919, when signs of a failing heart muscle were detected and he was advised to curtail his activities. In 1920 he developed pulmonary tuberculosis and moved to Texas for two years, returning cured of tuberculosis and with an increase in weight of 25 lbs, but with clinical evidence of a failing heart muscle, which ultimately incapacitated him so that he was compelled to retire from the practice of medicine. Electrocardiographic tracings made by Dr. Herrmann in various positions established a diagnosis of an adherent pericardium and chronic myocardial insufficiency. Response (A) in Nov., 1925, was taken while he was still attempting to practice medicine, showing a complete failure after the third step, with the appearance of a systolic murmur at the apex and a severe cough after the cardiorespiratory test. In a few months, decompensation was marked and he consented to remain in bed for two months, which was followed by gradual compensation. A cardiorespiratory test made Feb. 4, 1926, when his heart had clinically compensated gave a response of only 15 mm (no 93b in protocol) and the appearance of a systolic blow at the apex which had not been present before the test and which was followed by severe coughing and some dyspnea, demonstrated that compensation was not complete. His heart has compensated fairly well at present and he is able to get out, but slight exertion causes dyspnea and his response (B) to the cardiorespiratory test is still far below normal, while there has been a progressive diminution in his vital capacity.

Responses C and D (Case 123) An

executive 66 years old, weight 150 lbs, height 5 ft 6¼ in responded (C) normally to the cardiorespiratory test in 1925 during a routine physical examination, at which time no evidence of any abnormality of the cardiovascular system could be detected. In Sept., 1926, he had acute dilatation of the heart with auricular fibrillation, following influenza, which compensated sufficiently for him to resume his business activities. Cardiorespiratory test (D) made May 5, 1927, showed that the heart had not fully compensated and would not maintain its efficiency under strain. He was advised to curtail his activities, which he refused to do, and since then he has had three attacks of acute dilatation.

Responses E and F (Case 122) An executive 66 years old, weight 232 lbs, height 5 ft 11 in, has been under observation since 1915, when he showed signs of beginning failure of the myocardium from obesity. Nine holes of golf daily, on a level course, so toned up his heart muscle that he was free from any signs or symptoms of myocardial insufficiency, and a cardiorespiratory test (E) in July, 1927, gave proof that his heart could withstand strain satisfactorily. During the following winter he took a trip to Nassau where he ate and drank excessively, taking no exercise and gaining 12 lbs in five weeks. On his way home, in New York, he contracted a mild afebrile respiratory infection, confining him to bed for only two days, but followed by a cough. Upon reaching New Orleans he noticed that he lacked energy and was slightly dyspneic on mounting stairs. Examination April 2, 1928, revealed an irregular, rapid heart, no

murmurs, but extra systoles and pulsus alternans, while an electrocardiographic tracing made by Dr. Rosen disclosed auricular fibrillation, ventricular extra systoles and evidence of myocardial disease. Cardiorespiratory test (F) at this time showed a poor response with a great reduction in vital capacity since the former test.

Response G (Case 91) A realtor 58 years old; weight 155 lbs; height 5 ft 7½ in, consulted me Jan. 20, 1928, for an oppressed feeling in the chest while walking fast, associated with a peculiar tingling sensation in left arm and left hand. There was no actual pain. He had noticed the symptoms for the past two months whenever he walked fast, and he stated that when he stopped the sensation would pass off promptly. There was no enlargement of the heart and no murmurs were audible until he walked briskly up and down the examination room 20 times, when a soft systolic murmur became audible at the apex. The response (G) to the cardiorespiratory test suggested myocardial weakness and he was advised to go to Clifton Springs for treatment of his heart. Unknown to me he consulted a confiere of mine, not telling him of my advice, and the latter, not hearing a murmur, told him that his heart was normal. Three months later he had an attack of coronary thrombosis while walking on the street, followed by dilatation and hypostatic pneumonia, from which he died April 27, 1928. The response to the cardiorespiratory test and the increase in pulse rate, as well as the appearance of a systolic murmur at the apex after the test gave definite evidence of myocardial weakness.

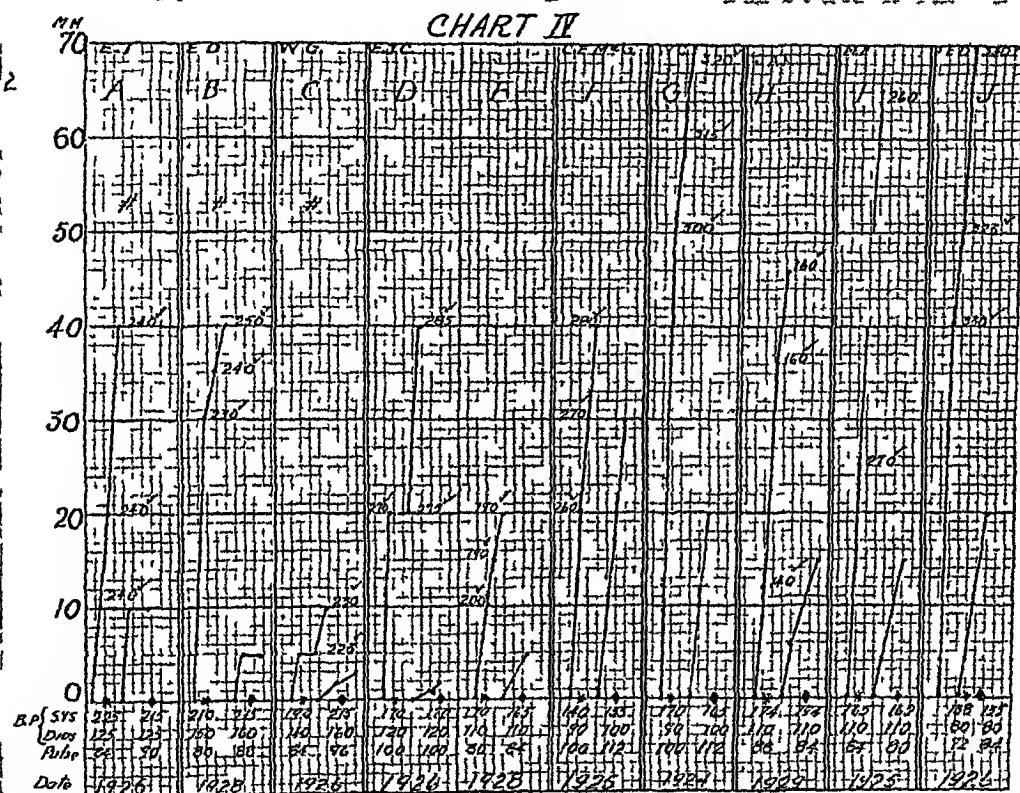
Response H (Case 95). An executive 49 years old; weight 203 lbs; height 5 ft. 11½ in, a mild diabetic, had been under observation since 1915 and repeated examinations of his cardiovascular system had never shown any abnormality until Nov 30, 1927, when he complained of a dull, aching pain in the cardiac region, not constant, but coming on usually after walking. The heart was not enlarged, there were no murmurs audible before the cardiorespiratory test (H) was run, which gave a poor response, with appearance after the test, of extra systoles and a soft systolic murmur at the apex. He was advised to go to bed and rest his heart, but instead, he went to Atlanta to attend a football game, where he had a severe attack resembling angina pectoris. In spite of rest and withdrawal from business activities, he continued to have anginal attacks and he died from coronary thrombosis Jan 27, 1930.

Chart IV. This chart is presented to show a tendency to overaction in blood pressure responses in cases of hypertension when the cardiac musculature is compensated.

Responses A, B, and C (Cases 96, 97, and 98) These all died from cerebral hemorrhage in two and one-half years, one and three-quarter years, and five months, respectively, after the tests were made. The poor response (C) of a man 53 years of age, with arteriosclerosis and a history of previous hypertension, denoted a failing heart muscle which coincided with his clinical picture. After compensation of his heart there was a return of hypertension, death following from cerebral hemorrhage.

Responses D and E (Case 99) A practicing physician 51 years of age, a case of hypertension secondary to chronic pyelonephritis, had a compensated heart in 1926 (D), symptoms of beginning loss of compensation in 1928

blood pressure of 180 mm results in a systolic blood pressure of 250 mm the danger of carrying out the test on cases of hypertension with initial blood pressure of 180 mm or over, is at once manifest and is to be discouraged



* Before Test. * After Test. * Cubic Inches of air blown through Spitzometer #2 Died

CHART IV Showing responses to the cardiorespiratory test on cases with hypertension with tendency to hyperactivity. A and B are normal responses. Both died from cerebral hemorrhage. C is a poor response showing weakened heart muscle. After heart had compensated patient died from cerebral hemorrhage. G, I, and J are hyperactive responses (see text).

(E), which disappeared on curtailment of activities. At present he is free from any symptoms of lack of compensation, while response (no 99c in protocol) denotes that he has full compensation. F, G, H, I, and J are well except for hypertension.

When one realizes that a rise of 70 mm in blood pressure over an initial

Chart V This demonstrates variable responses obtained on the same individual with varying amounts of air expired at varying pressures.

Responses A, B, C, and D An executive 56 years old, obese, weighing 211 lbs, unless instructed to breathe in full lung capacity, invariably presented a poor response at first test followed

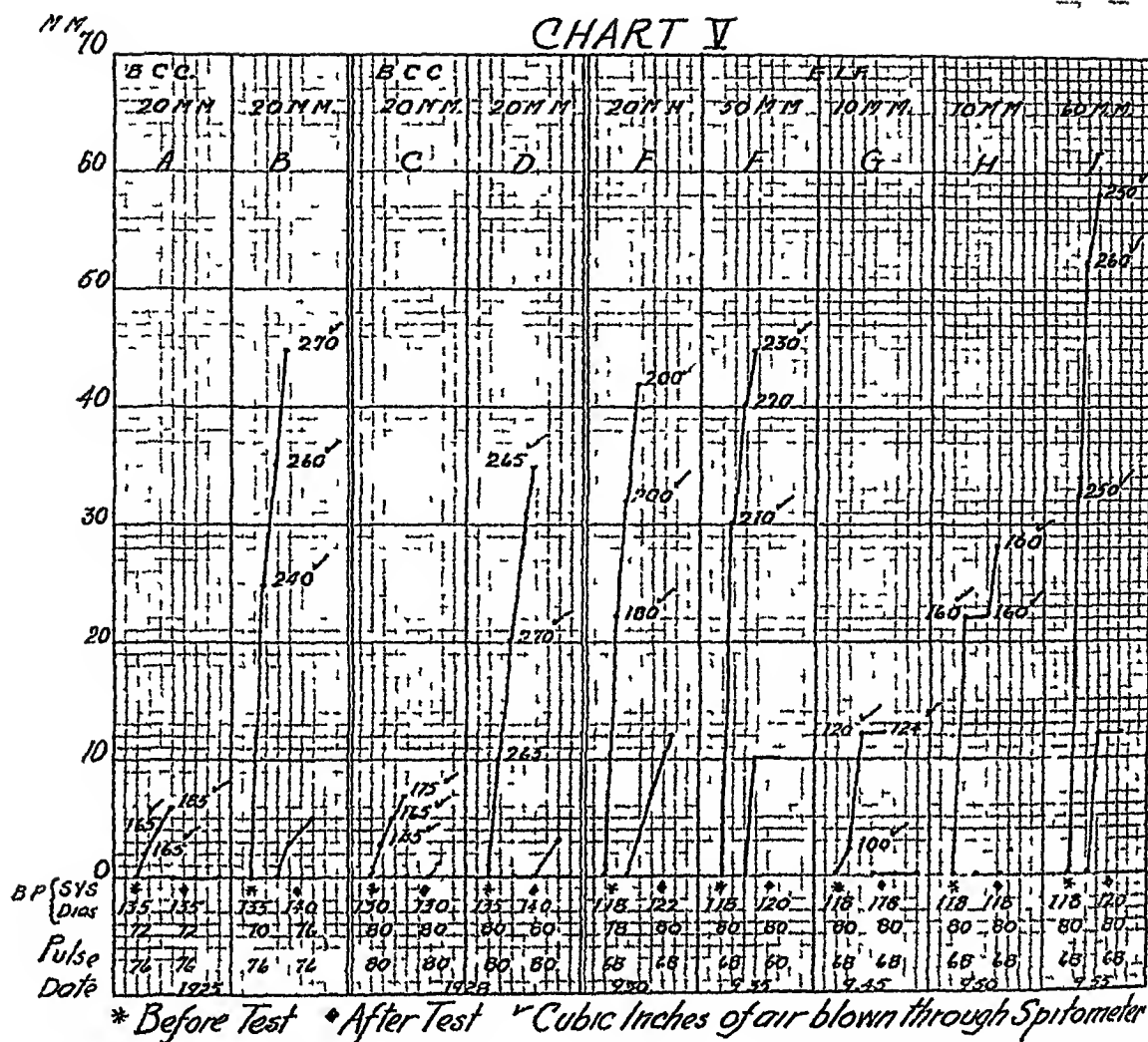


CHART V Showing responses to cardiorespiratory test when varying amounts of air are expired through spirometer at varying pressure (see text)

in five minutes by a normal response when he was properly cautioned

Responses E, F, G, H, and I A normal individual 35 years old, gave a normal response (E) with the proper technique, a slightly higher response (F) when the same amount of air was expired at a pressure of 50 mm instead of 20 mm. Responses (G and H) are below normal, obtained by expiring varying amounts of air at a pressure of only 10 mm, while (I) was obtained by extreme inspiration and expiration of 260 cubic inches of air at a pressure of 60 mm

The importance of cautioning the patient to breathe his full vital capacity at a constant pressure of 20 mm of mercury is manifest from an examination of these marked variations obtained on the same individual. I have experienced no trouble in getting the full co-operation of patients, excepting some women who seem to be unable to breathe deeply

SUMMARY

1. A modification of the original cardiorespiratory test, devised by Frost, is described, which, on account

of its simplicity, is applicable to routine clinical needs in evaluating cardiac cases

2 A protocol of 125 cases on whom 160 modified cardiorespiratory tests were performed, is presented

3 A poor response was obtained in 35 per cent, a fair response in 25 per cent, and a normal response in 40 per cent of the tests

4 The response to the test corresponded to the clinical evidence of the functional capacity of the heart

5 Charts of curves plotted from responses obtained in a number of cases observed over several years, are presented, showing graphically the improvement or decline in response to the cardiorespiratory test, correspond-

ing with the clinical picture of the case

6 A failure of the systolic blood pressure to respond in an increase of at least 20 mm denotes a weakened heart muscle, while a fall in the curve of the base line denotes a serious dilatation of the heart. The pulse rate, before and after the test has clinical significance

7 The cardiorespiratory test, when properly applied, is a valuable aid in the diagnosis and study of chronic myocardial insufficiency

8 The test should be used with caution on cases of marked cardiac dilatation, on cases with a history of angina pectoris, and on cases of hypertension

REFERENCES

¹BRITTINGHAM, HAROLD, and WHITE, PAUL D. Cardiac functional tests, Jr Am Med Assoc, 1922, LXXIX, 1901

²FROST, HAROLD M. A study of cardiovascular reaction to abnormal variations of intrathoracic pressure, Proc of the 33rd Annual Meeting of the Association of Life Insurance Medical Directors of America, 1922

³FROST, HAROLD M. The response of the cardiovascular system to respiratory exertion, Boston Med and Surg Jr, 1924, CXCII, 853. Also Hypertension and longevity, Boston Med and Surg Jr, 1925, CXCIII, 241

⁴HERRMANN, GEO R. Editorial—Some clinical tests for the estimation of circulatory-respiratory functional efficiency, Jr Lab and Clin Med, 1927, XII, 828

⁵EUSTIS, ALLAN. The Dwight-Frost car-

diorespiratory test as an aid in the early recognition of myocardial efficiency, South Med Jr, 1926, XIX, 585. Also The diagnosis and care of the failing heart muscle, New Orleans Med and Surg Jr, 1926, LXXIX, 50

⁶EUSTIS, ALLAN. The diagnosis of myocardial insufficiency. Results with a modification of the Dwight-Frost cardiorespiratory test, New Orleans Med and Surg Jr, 1929, LXXXI, 605

⁷SCHMITZ, H W. Vital capacity, respiration, frequency of pulse rate, and systolic blood pressure in heart disease, Arch Int Med, 1925, LXXVI, 628

⁸MACKENZIE, L F, WELLS, P V, DEWIS, E G, and YLVISAKER, L S. Flarimeter tests of circulatory fitness, Am Jr Med Sci, 1930, CLXXX, 372

Auricular Paroxysmal Tachycardia Caused by Digitalis

Report of a Case*†

BY ARTHUR F HEYL, B S., M D, *New Rochelle, N Y*

WHILE a patient, a man fifty years of age, suffering from congestive heart failure and hypertension, was being digitalized,** he returned to the clinic complaining of attacks of very rapid heart action. He stated that they were abrupt in onset and varied in duration from a few minutes to twelve or more hours. Some of these attacks were observed later in the clinic and thought to be auricular paroxysmal tachycardia. This was confirmed seven weeks after their onset (see EKG no 148, plate I, compare original EKG no 123, plate I). Since these attacks were assumed to be spontaneous an attempt was made to prevent them by more complete digitalization, following the suggestion made by Levine and Blatner¹. The attacks, however, became more frequent with this treatment and since a review of his history indicated that he had not been troubled by palpitation of this type before he first received digitalis, the possibility was evident that the digitalis might be the cause of his at-

tacks. He was then hospitalized for study to prove or disprove this theory.

HISTORY AND PHYSICAL EXAMINATION OF THE PATIENT ON ADMISSION TO THE CLINIC

The patient, a white male, fifty years of age, hospital clinic number 8739, was seen first on August 1, 1929. His chief complaint, primarily of an asthmatic nature, was shortness of breath during the night and early morning, or with effort. This began about a year previously, following an attack of acute bronchitis.

His past history was essentially negative, except for chronic bronchitis of fifteen years duration and pneumonia at the ages of thirty-seven and forty-five years. He also had a severe attack of "grippe" during the winter of 1928-29.

His family history was irrelevant.

Physical Examination The patient was a well-nourished, tall, erect male. A most striking over-development was noticed in his full, barrel-shaped chest, with sunken supraclavicular and suprasternal fossae. There was no visible or palpable enlargement of the thyroid gland. The more important physical findings were an emphysematous chest full of sibilant and musical râles and noticeable precordial and left axillary line bulging. There was slight dullness at both bases. Heart sounds both at the base and apex were distant and ill-defined. At the lower left sternocostal angle "apex sounds" were best heard of natural quality. No murmurs could be heard. The apex and pulse rates were equal at 110 and 120, depending upon the position of the patient, reclining or erect, respectively. The blood pressure was systolic,

*Received for publication, May 4, 1931.

†From the New Rochelle Hospital Cardiac Clinic, New Rochelle, N Y.

**Lederlé tablets and Davies, Rose and Company pills of the powdered leaf were the only preparations used with this patient.

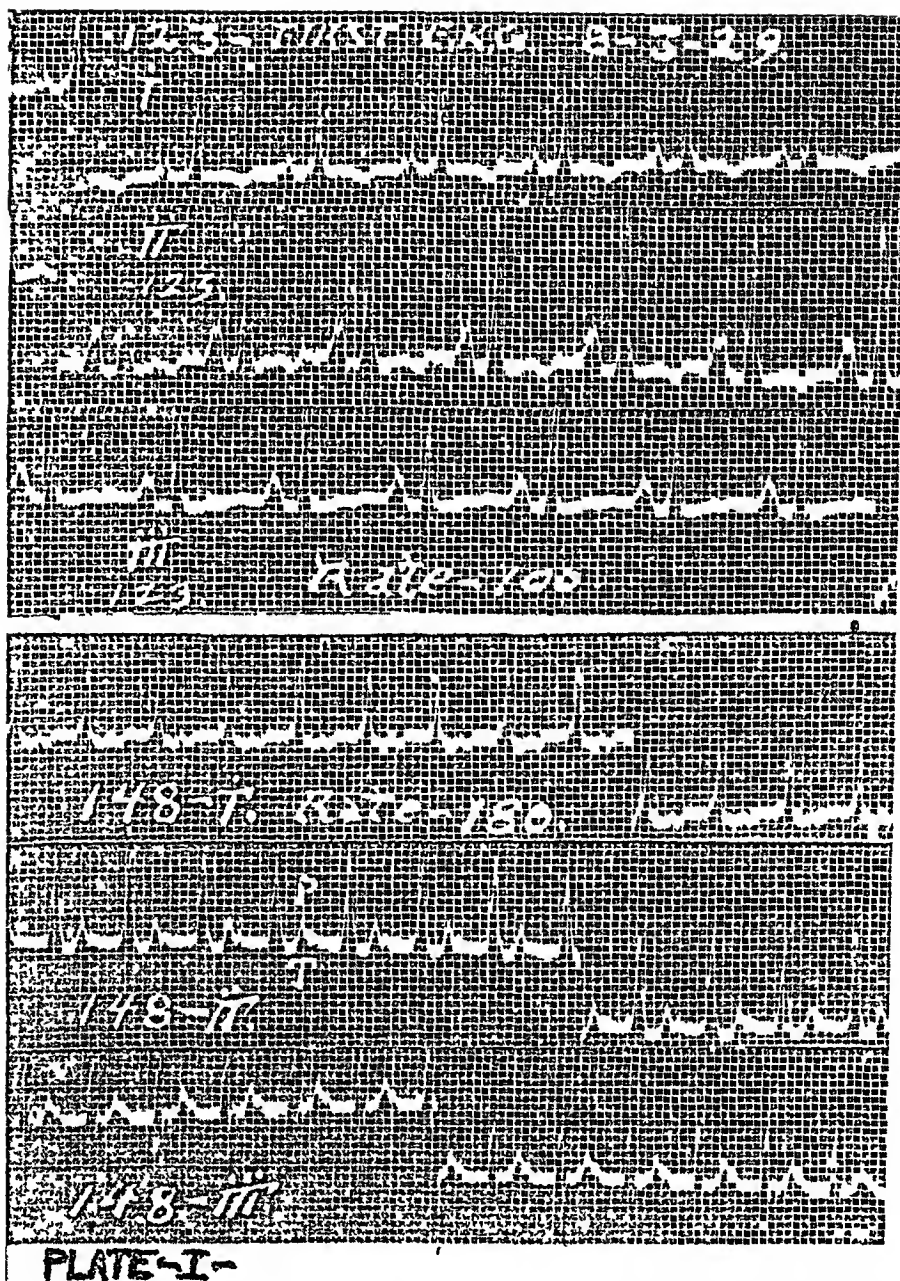


PLATE I EKG no 123, initial tracing before administration of digitalis showing left ventricular strain according to Barnes and Whitten⁷ No 148, rate 180 per minute, one of many recurrent attacks of auricular paroxysmal tachycardia after digitalization, on a maintenance dose of 0.1 gm a day

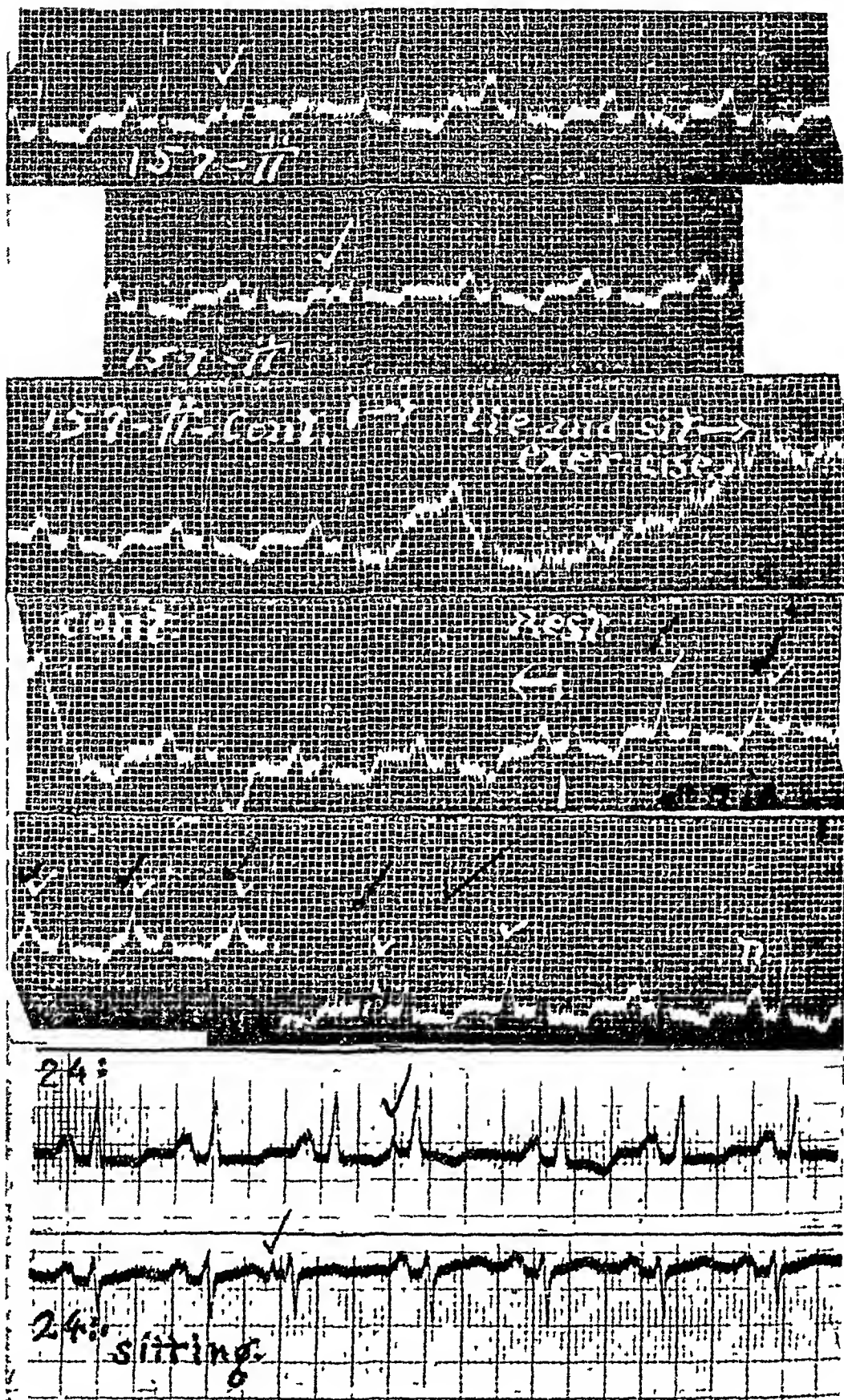


PLATE-II-

PLATE II EKG no 24, leads II and III show rare premature auricular contractions Note respiratory effect on S-wave Made ten days after discontinuing digitalis

170 mm, and diastolic, 130 mm of Hg. There was moderate edema of the ankles.

On August 24, 1929, radiographic examination of the chest at 77-inch focal distance revealed an aortic type heart with left ventricular enlargement, right interlobar pleural thickening, emphysema and bronchiectasis (plate XIII).

On Jan 16, 1930, his blood chemistry was normal, as were also his blood count and urine analysis. His blood Wassermann was negative.

A diagnosis was made of (1) Chronic heart disease associated with hypertension (pneumonia, chronic bronchitis, emphysema, bronchiectasis, asthma), (2) Greatly enlarged heart, (3) Regular sinus rhythm, occasional premature contractions, sinus tachycardia, (4) Early congestive heart failure.

Although indicating that his attacks occurred only when he was receiving digitalis (EKG no 183, plate III) the evidence during this hospitalization was not convincing, because he came to the wards after weeks of such medication and no control period free from the drug and attacks of tachycardia had prevailed. He was discharged without medication for the purpose of studying the condition further.

Tachycardia did not occur for three months until the patient on his own responsibility, because of dyspnea, took two grams of digitalis in ten days (0.2 gm a day). This resulted in an attack of tachycardia which lasted intermittently for four days.

AURICULAR PAROXYSMAL TACHYCARDIA INDUCED BY DIGITALIS THREE TIMES UNDER CONTROLLED CONDITIONS

After two more months without digitalis, in which period he had no attacks, he was again admitted to the hospital, this time in marked congestive failure. Following a rest of four days

in bed without improvement, digitalis was administered. It relieved him of failure but it also induced auricular paroxysmal tachycardia. Two subsequent observations with rest periods of seven days intervening, during which time digitalis was withheld, yielded additional proof that digitalis was the exciting cause of his attacks.

Period One (control EKG no 243, plate IX) When 1.3 grams of digitalis had been given in twenty hours, the patient complained of palpitation and an auricular paroxysmal tachycardia was revealed (no 247, plate IX). Digitalization was continued to the full calculated dose of 2.9 grams in three days and then discontinued because of a 2:1 block, with a rapid ventricular rate. The abnormal auricular rate continued (no 248, plate IX). There were no other toxic symptoms. Three days later, transient "paroxysmal" attacks occurred as the result of ventricular response to each auricular impulse (no 250, plate IX). Subsequently, the patient's usual sinus tachycardia prevailed, rate of 100 to 110 per minute (no 251, plate IX and no 252, plate X).

Period Two An interval of seven days elapsed without the administration of digitalis. After the patient had received 0.9 gram in twelve hours, he was awakened by tachycardia two and one-half hours following the third dose of 0.3 gram. This occurred at night and no tracing was obtained. Due to an additional and final dose of 0.3 gram four hours later, a 2:1 block with an auricular rate of 220 per minute resulted (nos 254 and 255, plate X). In the next four days, transient periods occurred, however, when the auricular

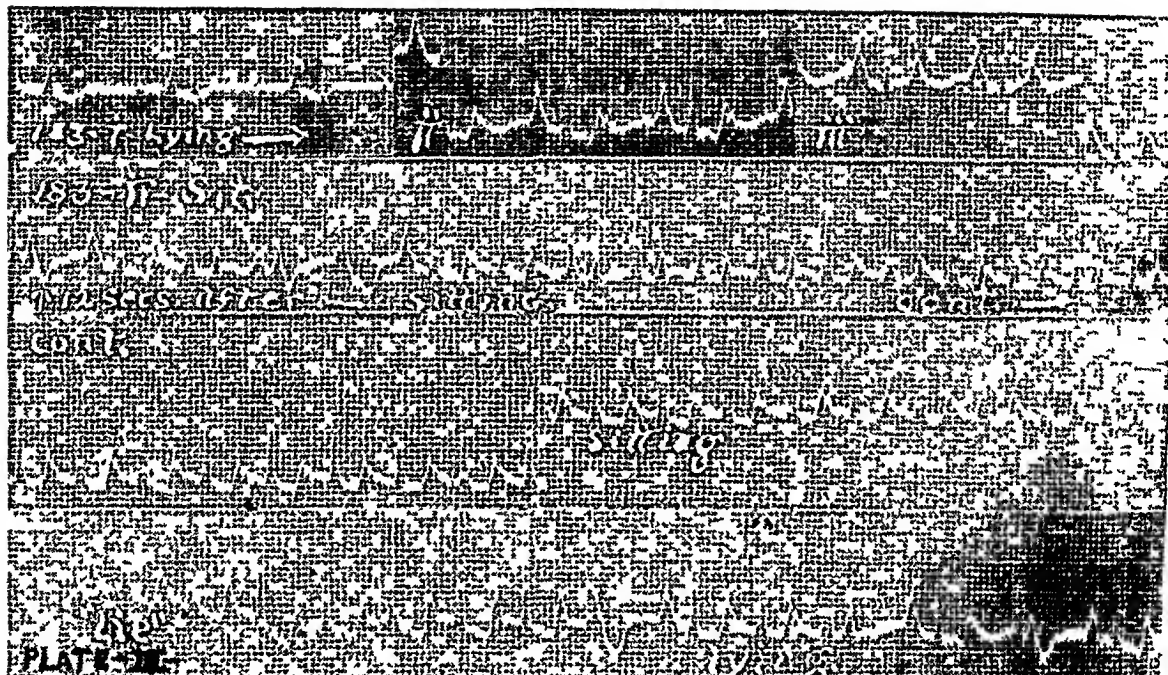


PLATE III The last three strips are continuous

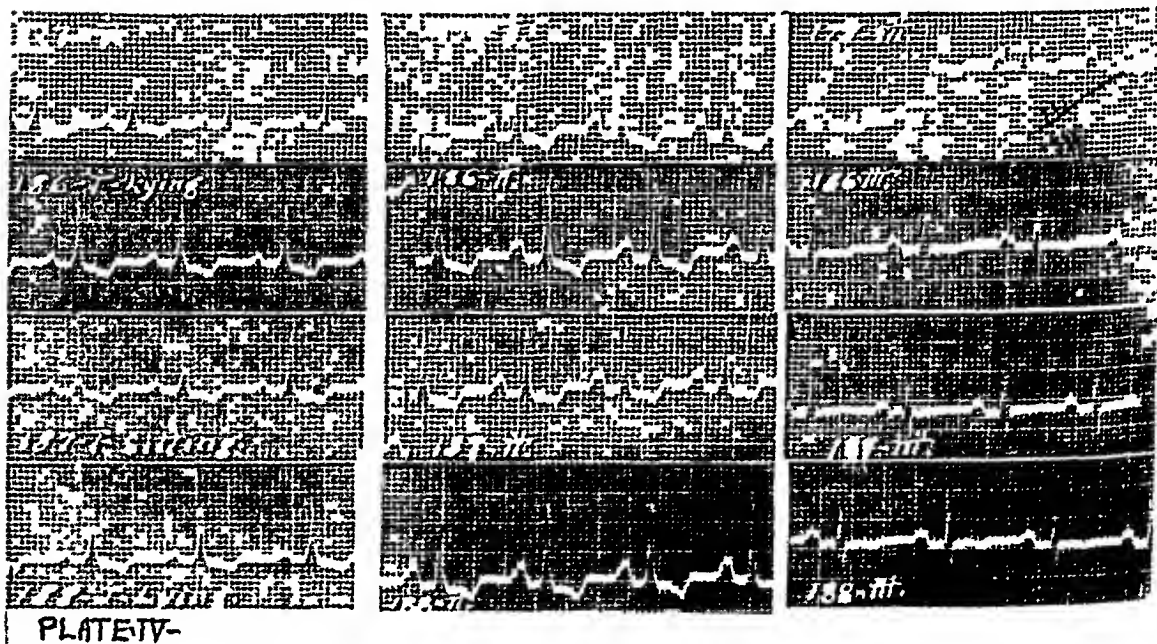


PLATE IV EKG no 177, control 5 days prior to 183, nos 186, 187, 188 taken during 5-day interval after 183 when digitalis had been temporarily discontinued Compare postural effects in leads III

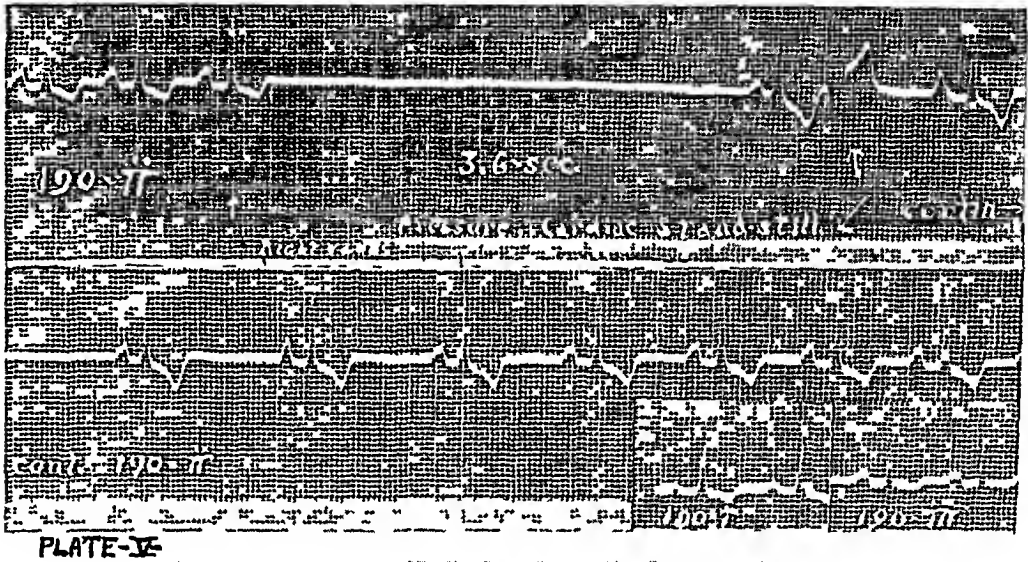


PLATE V Vagus pressure released at end of "stand-still"

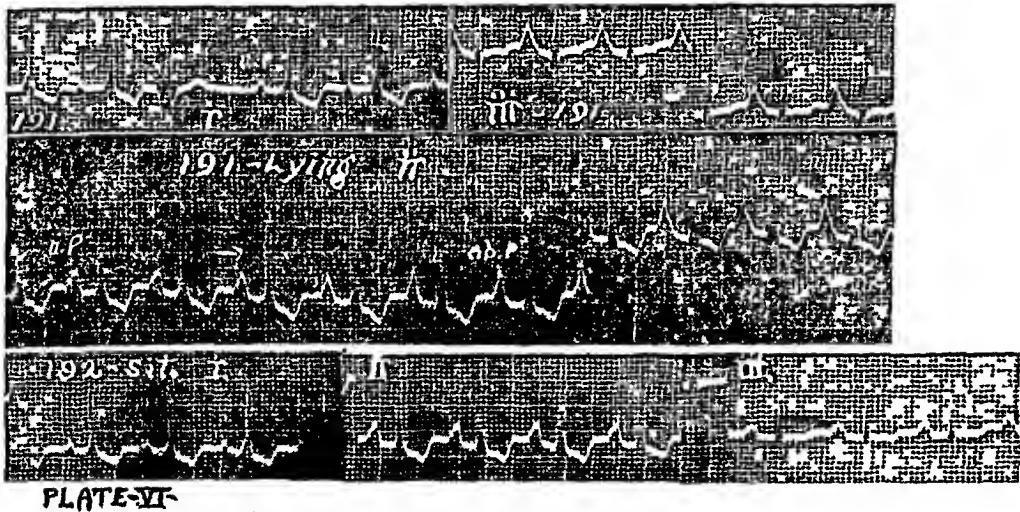


PLATE VI EKG no 191, control made 20 hours after no 190 showing transition in lead II from the "normal" to the ectopic P-waves and an increase in rate No 192, control four hours later

tachycardia was attended by a 1:1 rhythm alternating with block (EKG nos 256 and 261, plate X). Thereafter, for three days a "normal" rate and rhythm were constant (nos 262, 263 and 266, plate X)

Period Three Another week having intervened since the administration of digitalis, 0.9 gm was given within ten hours. Three hours after two-thirds of this amount had been taken, he had a regular sinus rhythm, with a "normal" rate (no 267, plate XI). Three and three-quarters hours after the final third (0.3 gm), the patient complained of tachycardia (no 268, plate XI). Block again followed for two days (nos 269, 270, 271 and 273, plate XI) and on the second and third days after digitalis had been discontinued, short periods of palpitation (1:1 rhythm) were again observed by the patient and internes but no electrocardiograms were taken. A "normal" rate with regular sinus rhythm subsequently prevailed (nos 274, 275, not reproduced; and 276, plate XI, recorded on succeeding days)

ADDITIONAL OBSERVATIONS

In an attempt to obtain more information relative to the origin of this patient's paroxysmal attacks and the relation to them of digitalis, additional observations and tracings were concurrently made. The effect of vagus stimulation by compression and eye-ball pressure, of exercise, of forced coughing; of holding a deep inspiration; all before and after the administration of digitalis, and the effects of amyl-nitrite inhalation, when no digitalis had been given, were studied.

Vagus Stimulation At this time,

no digitalis having been administered for forty-six days, right vagus compression, left vagus compression, right then left eye-ball pressure, all failed to alter materially the control electrocardiogram (no 293, plate XII)

During digitalis administration, vagus stimulation gave results which varied apparently with the dosage. Right vagus compression produced cardiac standstill for 3.6 seconds and slowing subsequently to a rate of 40 and 50 per minute, after the patient had received 1.2 gms of digitalis in divided doses during a period of twenty-five hours. The P-waves were sharpened and the T-waves deepened (no 190, plate V)

Following an increase in the daily dose of digitalis, vagus pressure failed to produce cardiac standstill. Sharpened P-waves, lengthened P-R intervals and a 2:1 block did result (no 193, plate VII)

With still another increase in the daily dose, the only result of left vagus compression was expressed by sharpened P-waves. Right vagus compression at first almost completely obliterated the P-waves and reduced the P-R interval from 0.20 to 0.12 second (nodal rhythm; dislocation of pacemaker). The T-waves were not affected as before (no 198, plate VIII). Space does not permit reproduction of the electrocardiogram but in this same tracing right and left eye-ball pressure separately gave the same results as right vagus (neck) compression.

At another time, two days after 1.2 grams of digitalis had been given in 18 hours, a run of auricular paroxysmal tachycardia was interrupted by right

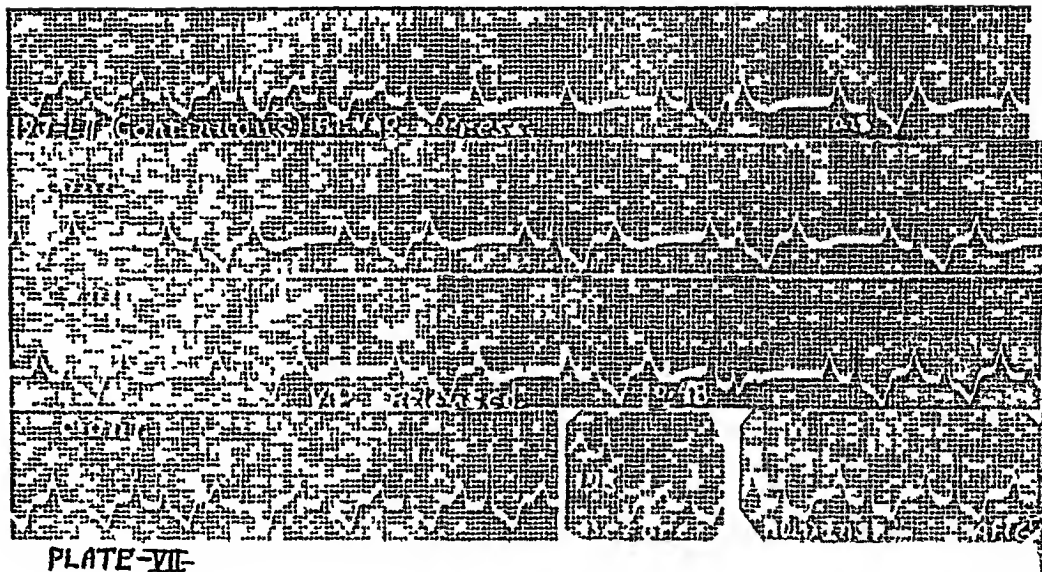


PLATE VII

PLATE VII Note the gradual transition in the last strip from ectopic to normal rhythm following vagus release

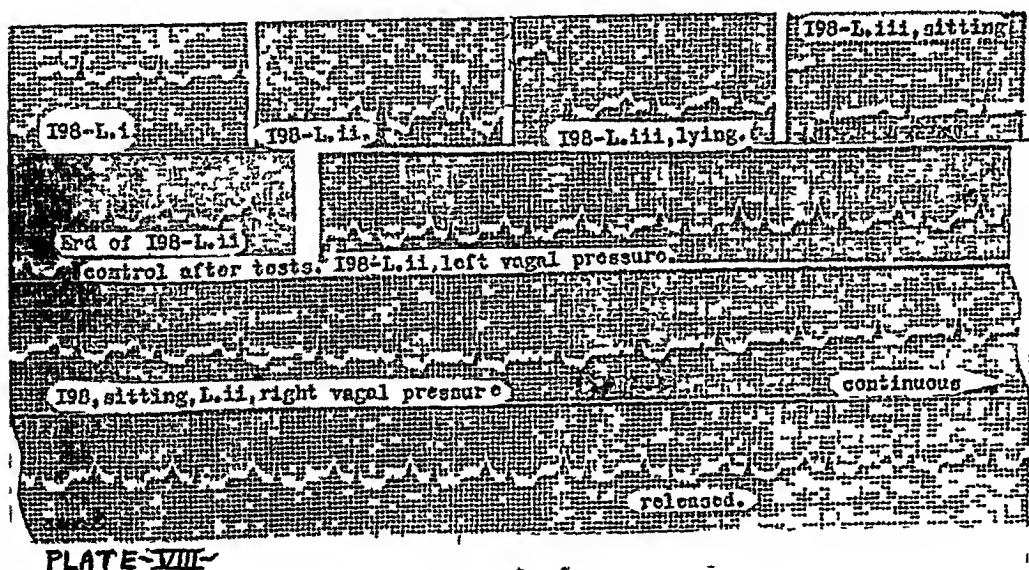


PLATE VIII

PLATE VIII

vagus pressure and resulted in 5:1, 3:1, 2:1 block (no 256, plate X)

The only effect of exercise after digitalis had been withheld for forty-six days was to increase the rate from 100 to 110 per minute. After digitalis had been administered, exercise resulted in tall, sharply pointed, ectopic P-waves (no. 157, plate II) like those appearing in his first recorded auricular

previously having been administered (no 267, plate XI). This effect also was observed when no digitalis had been given.

Holding a deep inspiration induced the ectopic P-waves, following the administration of digitalis (no 193, plate VII). When digitalis had been withheld for many days, this could not be duplicated.

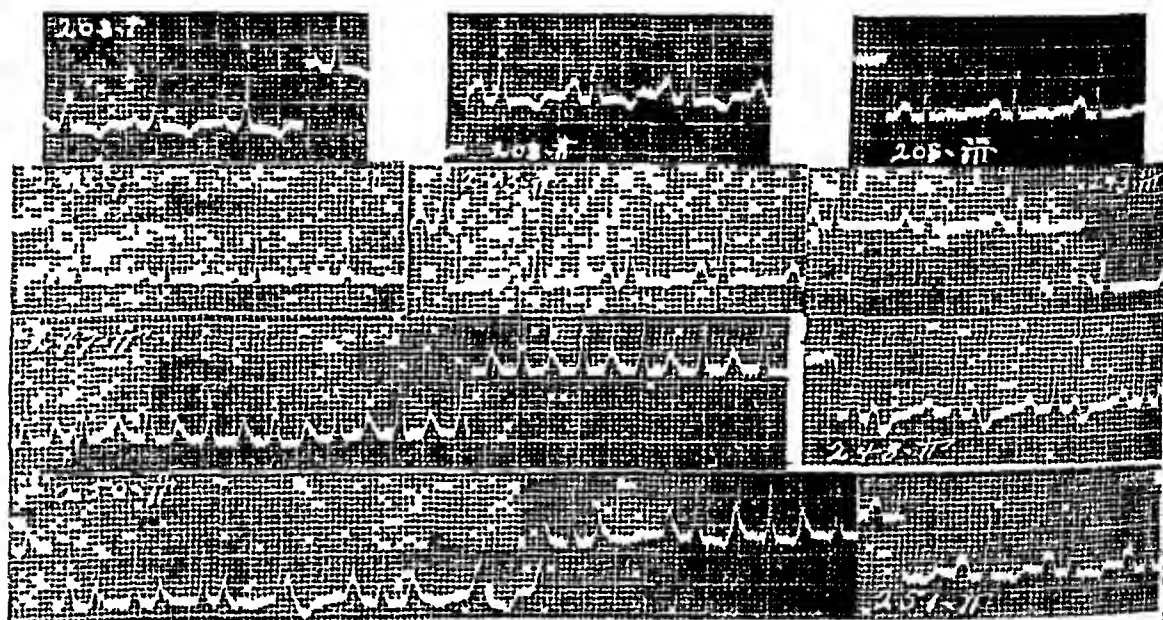


PLATE-IX

PLATE IX EKG no 208, control after 1 month without digitalis No 247, rate 150 per minute

paroxysmal tachycardia (no 148, plate I). On another occasion, the effort of sitting up in bed transformed an auricular paroxysmal tachycardia, with a 2:1 a-v block, auricular rate of 180 per minute, to the same type of tachycardia with auricular and ventricular rates of 150 per minute. Reclining again resulted in the original block (no 183, plate III). These variations were immediately repeated and recorded three times with the same result.

The act of coughing produced the characteristic ectopic P-waves, digitalis

The only effects of amyl-nitrite inhalations six days after digitalis had been discontinued were an increase in the rate from 100 to 120 per minute and slight elevation and sharpening of the P-waves (no 277, plate XII).

SPONTANEOUS PREMATURE CONTRACTIONS

Spontaneous auricular premature contractions were recorded in only two of the forty-five tracings from this patient made during more than one year's observation. In the first in-

stance they occurred during digitalis administration (no 157, lead II, plate II) Nine months later, when no digitalis had been given for ten days, such premature contractions of spontaneous occurrence were recorded (no 24, leads II and III, plate II)

Spontaneous ventricular contractions also were rare (no 191, lead I, plate VI, no 247, lead II, plate IX)

COMMENTS

A thorough search of relevant work published since 1912 failed to reveal an instance of auricular paroxysmal tachycardia that was definitely proved to be due to digitalis

Bastedo² has reported a case of paroxysmal (auricular) tachycardia which he considered as produced by digitalis, but the origin of this disturbed cardiac mechanism is not accurately demonstrated since the tracings are polygrams

Howard³ presents one case and cites eleven others from the literature of double, auricular and ventricular, tachycardia due to digitalis He published only one electrocardiogram from his patient in which he found co-existing auricular and ventricular tachycardia with rates of 195 and 160 respectively The P-waves, as he states, are inverted and therefore "this represents an auricular tachycardia originating in an ectopic focus in the auricle", but the repetition of such production was not obtained because of the patient's death It is not possible to state with certainty that the digitalis was the cause

Luten⁴ reported four patients with normal cardiac mechanisms in whom temporary auricular tachycardia devel-

oped with atrioventricular dissociation after receiving large amounts of digitalis No mention is made of their being paroxysmal in type, having their origin in ectopic foci Reporting an electrocardiogram of his Case 3, he expressed the belief that the rhythm originated in the auricle "Auricular waves, however, cannot be clearly distinguished, either in this paroxysm or in that part of the record which immediately precedes it"

With the exception of Howard's case none of the eleven others which he reported, including Luten's, apparently conform to the accepted definition of paroxysmal tachycardia, having its origin in an ectopic auricular focus (Lewis⁵), and in none of them do repeated cause and effect observations make it possible to state with certainty that the digitalis induced the attacks

While in our case a tracing was not obtained showing the actual onset of a usual attack, it was observed clinically to be abrupt and furthermore, the ectopic origin of the P-waves is clearly evident

A midday control tracing (no 191, lead II, plate VI), taken by the technician, does show the gradual development of the ectopic P-waves and a progressive shortening of the T-P interval with an increasing rate This no doubt is the manner in which the paroxysmal attacks originate in this patient and from which the 2:1 block at a higher stage of digitalization results Further, in the last six complexes of no 193, plate VII, following the release of right vagal pressure, is shown the gradual relinquishment of such an ectopic rhythm corresponding

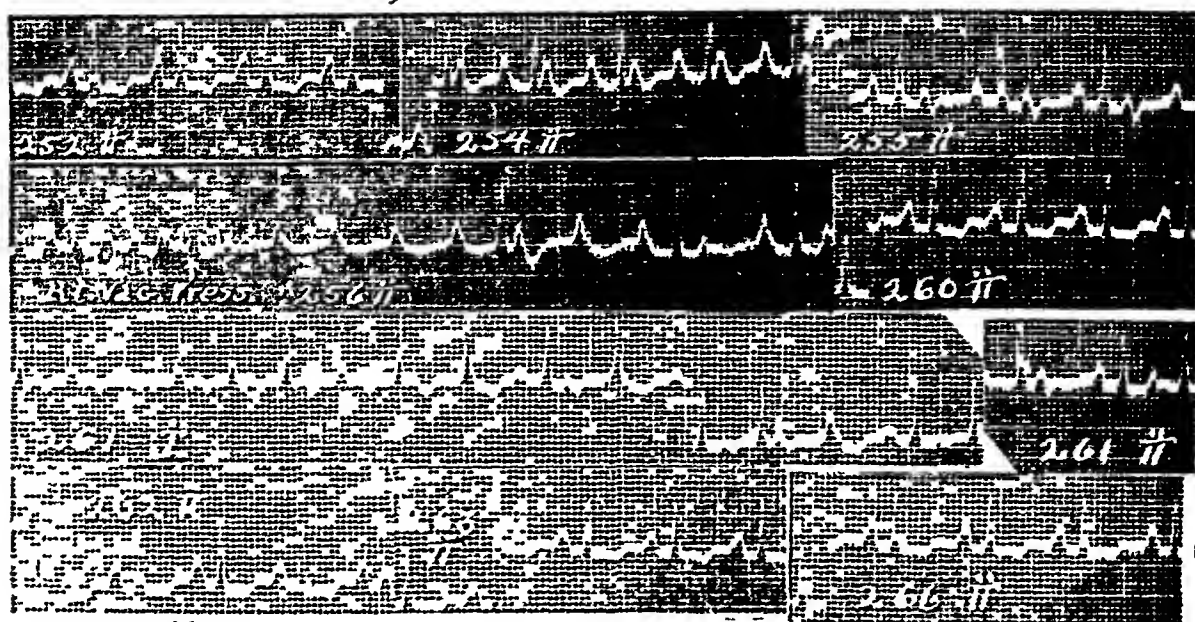


PLATE-X

PLATE X EKG no 254, auricular rate 220 per minute No 255, auricular rate 180 per minute

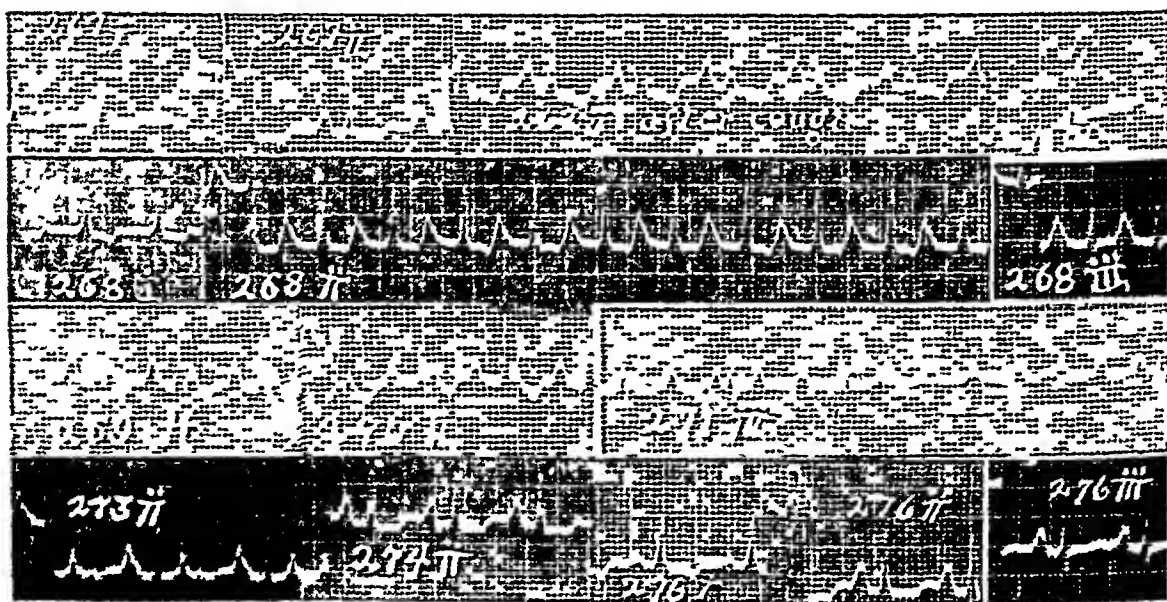


PLATE-XI-

PLATE XI EKG no 267, three hours after administration of total of 0.6 gm digitalis No 268, three hours and forty-five minutes after final total administration of 0.9 gm digitalis

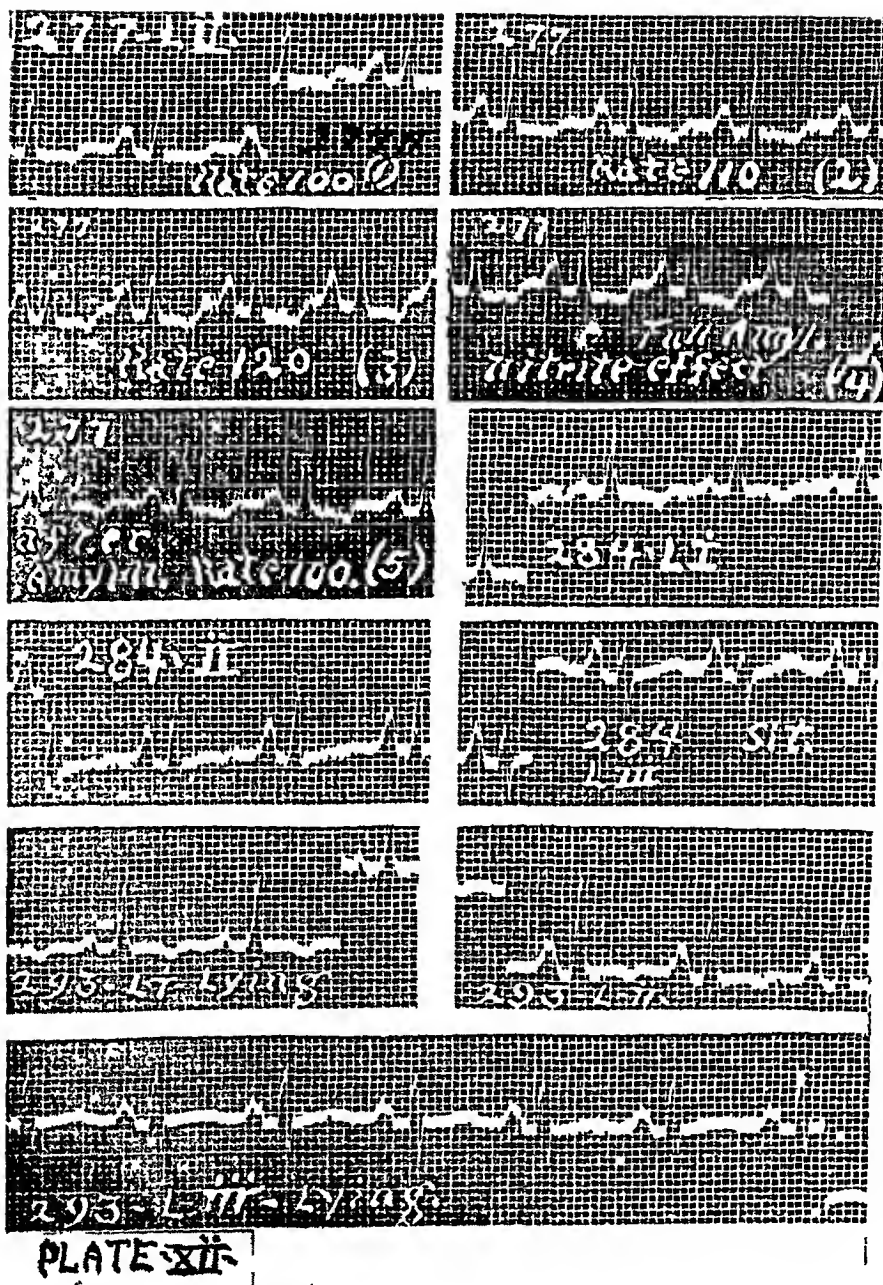


PLATE XII EKG no 284, control 26 days after discontinuing digitalis. Note postural and respiratory effect on deviation of electrical axis as compared with No 293 twenty days later

to an end phase of his auricular paroxysmal tachycardia

In electrocardiogram no 183, plate III, while the auricular paroxysmal tachycardia is present with a 2:1 block, the onset of 1:1 rhythm, the release of block, is nicely shown, occasioned by sitting up in bed. The interruption of such ventricular response, re-establishment of a 2:1 block, is also shown. Such transitions likewise are seen in no. 250, plate IX, without previous effort

SUMMARY AND CONCLUSIONS

1 Presented with an adult male, past middle age, having hypertension and congestive heart-failure, it was observed more than nine times that the digitalis, which gave him relief from his symptoms (dyspnea, cough, passive congestion, edema) concomitantly induced auricular paroxysmal tachycardia followed by a 2:1 block, in which the abnormal auricular mechanism prevailed

2 These abnormal rates and rhythms occurred only as the result of digitalis administration

3 The writer was unable to find any reference in the literature to such a mechanism due to digitalis so conclusively proven

4 Various methods, such as effort, deeply held inspirations, forced coughing and amyl-nitrite inhalations were utilized in an attempt to induce the attacks, both in the presence and in the absence of digitalis administration. When no digitalis was being administered they were consistently unsuccessful. Ectopic P-waves like those occurring with his attacks were, however, obtained, but in only one instance, by

forced coughing, when he was free from the drug

5 Various attempts were made to ascertain the effects of vagus stimulation. While he was free from digitalis, external vagus stimulation did not produce any change in the cardiac rate or rhythm nor any electrocardiographic variations. Neither did digitalis alone, even in full dosage, slow the rate as would have been true had it acted directly on the vagus. But the heart at different times, affected by different amounts of digitalis, was rendered susceptible to external vagus stimulation in effects varying from complete cardiac standstill to 5:1, 3:1, 2:1 block, with auricular slowing; to nodal rhythm and no slowing, or to ectopic P-waves and no slowing, depending on the size of the dose. These vagus responses, occurring only in the heart affected by digitalis, correspond to the method of Weil⁶ for determining the onset of toxic digitalis effects

6. Spontaneous premature contractions were exceedingly rare, either of auricular or ventricular origin, in the presence or absence of digitalis administration

7. No toxic symptoms due to digitalis ever occurred, even with full calculated dosage, except the abnormal mechanisms previously mentioned.

8 The practical significance of these observations is, as others have noted, that graphic methods are especially valuable for diagnosis in patients with sinus tachycardia, particularly in those who need and are receiving digitalis. In this instance even mild doses repeatedly resulted in auricular paroxysmal tachycardia, with or without a

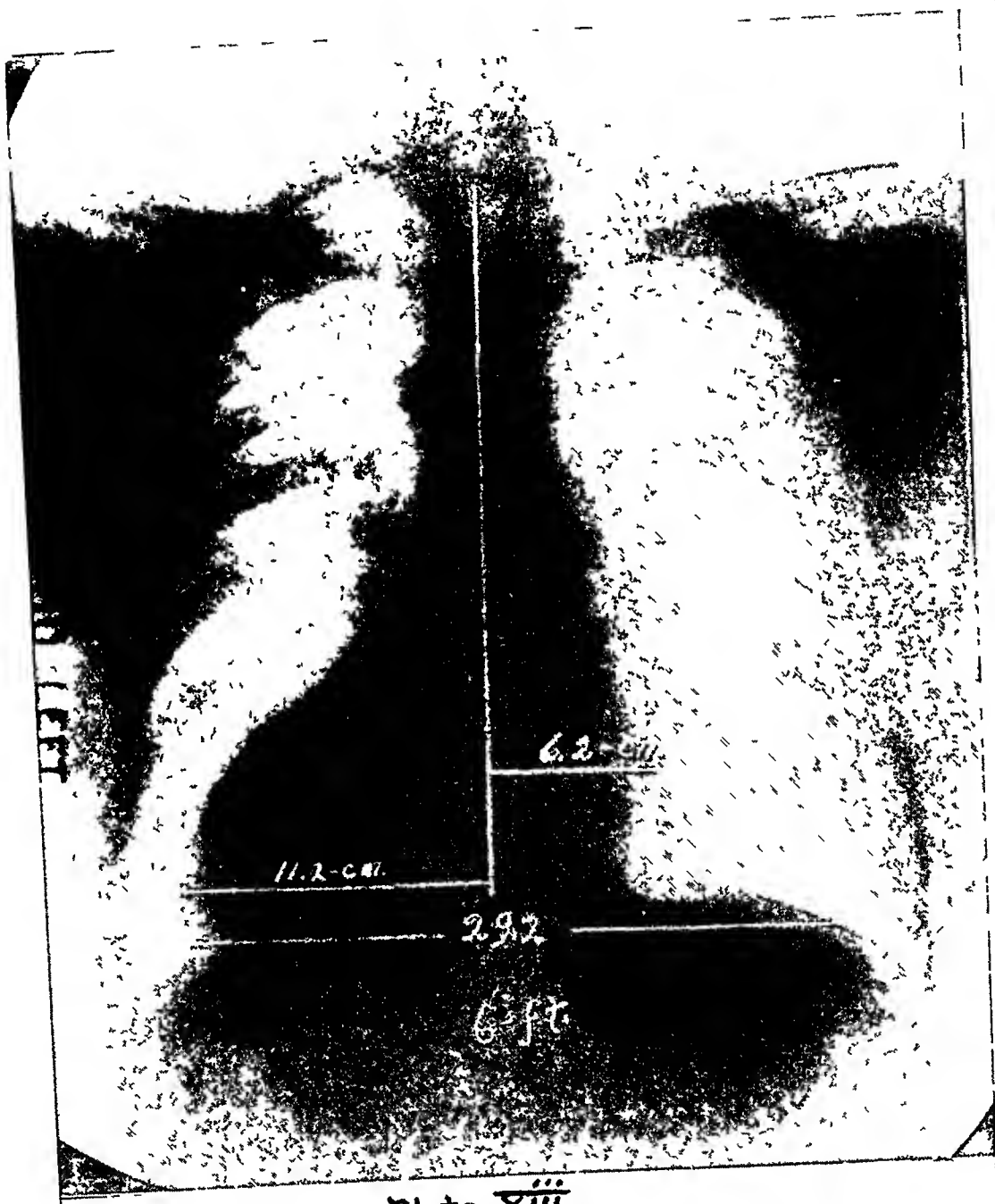


Plate XIII

2:1 block with a rapid ventricular rate, which without electrocardiographic control, might naturally have led to the futile use of more digitalis and increased toxicity in an effort either to slow the ventricular rate or to prevent

the often recurring "clinical" auricular paroxysmal tachycardia.

I am indebted to Dr Harry Gold of New York for his helpful criticism and suggestions in the preparation of this report

REFERENCES

- ¹LEVINE, SAMUEL A., and BLATNER, HARRY
The treatment of paroxysmal auricular tachycardia, *Am Jr. Med Sci*, 1926, CLXXII, 660-664
- ²BASTEDO, WALTER A. · The signs of overdosage in digitalis administration, *Am Practitioner*, 1912, XLVI, 609
- ³HOWARD, T Double tachycardia Co-existing auricular and ventricular, due to digitalis, *Am Jr Med Sci*, 1927, CLXXIII, 165-168
- ⁴LUTEN, D Clinical studies of digitalis · II, III, *Arch Int Med*, 1925, xxxv, 74-79
- ⁵LEWIS, THOMAS The mechanism and graphic registration of the heart beat, p 240, 3rd, Ed, 1925, Shaw and Sons, Ltd, London
- ⁶WEIL, ALFRED Beitrage zur klinischen Elektrokardiographie II Mitteilung, Ergebnisse des Vagusdurch-Versuches, Deutsch *Arch f klin Med*, 1916, CXIX, 39
- ⁷BARNES, A R., and WHITTEN, M B Study of T-wave negativity in predominant ventricular strain, *The Am Heart Jr*, 1929, v, 14

Hospital Diets

“A ROUTINE hospital diet should no more be a mysterious affair than a prescription for the pharmacist. If its existence is at all justified, it should be based on the same rational principles that govern all other forms of therapy. A routine diet should have a purpose, a plan, and an objective; it should be based on the laws of nutrition, it should contemplate specific needs in the patient, it should have its indications and its contraindications. Properly employed, the routine hospital diet becomes a convenience to the physician, to the administrative staff, and to the patient.”—(From *Clinical Dietetics*, by HARRY GAUSS, M S, M D, F A C P, C V Mosby Company)

Medical and Surgical Problems Associated With Coronary Sclerosis*†

BY ARLIE R. BARNES, M D , F A C P , *Rochester, Minn*

TODAY, beyond doubt, heart disease is the "captain of the men of death." Coronary sclerosis accounts for a large proportion of deaths from heart disease. This might not be so depressing if death from coronary sclerosis came after a long life, but too often the condition claims its victim when he is in his prime and when elsewhere in his body there is no evidence of serious deterioration. There is a distinct need for a review of the common aspects of this disorder, to bring into sharper view its clinical manifestations, and to call attention to the bearing the newer knowledge has on the solution of the many problems which coronary sclerosis presents.

Additions have been made to knowledge of the normal coronary circulation and its pathologic changes. Spalteholz, Gross, Whitten and Campbell have greatly enlarged knowledge of the normal coronary circulation. The distribution of the branches of the right coronary artery to the basal and posterior portion of the left ventricle, described by these writers, has not received the attention it deserves and the result has been failure to appreci-

ate the frequency with which that portion of the left ventricle may be the site of infarction. The work of Whitten disclosed striking variation in the structure of the coronary arteries, depending on whether they are distributed to the right or the left ventricle. Branches of either the right or the left coronary artery, going to the left ventricle, leave the main trunks at right angles, penetrate the myocardium, and when they reach the endocardial surface turn at right angles, ending in a mass of fine arterioles. This has the effect of fixing the main trunks at the points of origin of the penetrating branches. When arteriosclerosis occurs, with resultant lengthening of the vessel, it leads to more or less angulation of the main branches at the points of fixation. This, together with the disproportionate degree of arteriosclerosis that occurs about the mouths of these penetrating branches makes for greater narrowing at these points, and increases the liability to thrombosis of the main branches.

On the other hand, the smaller branches of the right coronary artery, going to the right ventricle, spread out in the same plane as the main divisions from which they arise, and these small branches anastomose freely. This may be one explanation of the almost total

*Submitted for publication, May 7, 1931.

†From the Division of Medicine, The Mayo Clinic, Rochester, Minnesota.

absence of acute infarction in the right ventricle

Gross is of the opinion that with advancing years there is increasing impoverishment of the circulation through the right coronary artery as compared with that through the left. Whitten's studies did not support that view, for he wrote "The portion of the right coronary artery which supplies the left ventricle keeps pace in its vascular development with the left coronary artery in successive decades." Certainly if myocardial infarction can be considered as an index of the inadequacy of the coronary circulation, the overwhelming frequency of its occurrence in the left ventricle indicates failure of the circulation to the left ventricle with advancing years rather than failure of the circulation of the right ventricle.

Comparative anatomy shows that the presence of coronary arteries is associated with the development of a cortical myocardium²⁵. In the lower animals the blood circulates in the intratriabecular spaces, through the whole thickness of the cardiac walls. Higher in the animal scale, in reptiles, the inner trabecular part of the myocardium retains a thebesian, sinusoidal circulation while there is a definite coronary circulation to the cortical portion of the wall. There is free communication between these two systems of circulation. In the rabbit "the thebesian, intertrabecular circulation is much reduced, but it retains its connections with the coronary capillary system, and persists as an integral part of the adult myocardial blood supply."²⁵ It is not surprising, therefore, that Wearn²⁶ and his co-workers²⁷ have been able to demonstrate in man communication of the

coronary circulation with the chambers of the ventricles, either by way of the thebesian vessels or by means of coronary capillaries communicating directly with the ventricular chambers. Cases of bilateral occlusion of the ostia of the coronary arteries have been reported. The occlusions presumably had occurred gradually, and probably had existed for some time prior to the attack. It is apparent that in such cases the circulation to the heart had to take place by way of the thebesian veins, through their connection with the coronary circulation.

Besides the thebesian circulation, there is a variable degree of pre-capillary anastomosis of the coronary arteries. The coronary arteries are no longer considered to be strictly end arteries. The degree of anastomosis appears to have individual variation, and on this account it may be assumed that some persons are inherently endowed with a coronary circulation which is little able to cope with acute closure of a coronary vessel. The degree of anastomosis tends to increase with advancing age, and that may be one reason why fewer persons more than seventy years of age die of acute coronary occlusion than those of an earlier age. The rate of obliteration of coronary vessels also plays an important part in the extent to which anastomotic channels develop. The studies of Oberhelman and LeCount may be interpreted to mean that in those normal hearts in which there is a negligible amount of anastomosis of the coronary vessels and in which the arteries are essentially end arteries, sudden occlusion of an artery is likely to result in sudden death. In hearts

which are fairly normal, and which possess rich collateral circulation, sudden occlusion of a vessel may be well tolerated, may lead to infarction and subsequently to healing by fibrous replacement. In hearts with slow development of sclerotic narrowing, abundant coronary anastomosis is likely to occur and it is in this group that sudden coronary occlusion is best tolerated. As Benson remarked, "It must be concluded, then, that arteriosclerotic narrowing of the coronary arteries as related to thrombosis of these vessels, is not an unmitigated evil in that it gradually prepares them for the catastrophe that is to come."

The pain observed following acute occlusion of a coronary vessel certainly appears to have a definite pathologic basis. The major difference between this pain and that which is unassociated with coronary occlusion is probably one of degree only. Atheroma of the coronary arteries is the common lesion found in cases of coronary sclerosis, and the pain is considered to be the result of anoxemia¹⁴ due to a blood supply "suddenly insufficient for the needs of the heart muscle for the moment"¹⁰. In certain cases of angina pectoris, sufficient changes in the coronary vessels to account for inadequate blood supply are lacking, and a paroxysmal vasomotor spasm has been postulated to explain these cases. The demonstration by Anrep and Segall that there is vasomotor control of the coronary circulation in the dog might be regarded as supporting the conception of such a mechanism of production of pain. However, the explanation of anginal pain on the basis of paroxysmal vasomotor spasm is at present devoid of

any reliable clinical or experimental proof.

Angina pectoris is sometimes observed in cases of pernicious anemia,³³ hyperthyroidism,¹² and paroxysmal tachycardia.⁶ There are evidences that in many of these cases the coronary vessels are not the seat of notable disease. It seems highly probable that the factor productive of pain, common to all these mechanisms, is a coronary circulation that is inadequate in the amount of oxygen furnished to the cardiac muscle. It is important to note that angina pectoris arising from any of these conditions is usually overcome by correction of the underlying disturbance. Consequently, the prognosis of angina pectoris, when it arises from these causes, is much better than when the condition has its origin in coronary sclerosis.

Coronary sclerosis affects the main branches of the coronary vessels, diminishing in degree as the smaller branches are approached. Even in cases of malignant hypertension, the arterioles are less affected than are the arterioles elsewhere in the body.¹⁵ The intima is eccentrically thickened, and atheroma is the common lesion. This may lead to gradual occlusion of a large vessel, and subsequent canalization of the occluded portion occurs rather commonly. Thrombi frequently form at the site of ulcerating and calcareous atheromatous plaques, leading to sudden occlusion of the vessel at that point. Syphilis at present is regarded as having little significance in the production of disease of the coronary vessels, except at their origin, where syphilitic aortitis frequently leads to occlusion of the ostia.

The myocardium, in cases of coronary sclerosis, may not exhibit changes, or it may be involved in varying degrees of myocardial necrosis and replacement with fibrous tissue. Diffuse myofibrosis, interspersed with fairly normal muscle fibers, is found in the region supplied by a severely diseased vessel, and probably results from gradual occlusion of the vessel. This process is considered to be due to chronic infarction, and its degree will be influenced by the amount of injury that exists in the vessel, and by the extent of the development of accessory channels of circulation. Hypertrophy of the heart is present in the majority of cases of coronary sclerosis, but this is probably the result of the frequent association of the condition with hypertension. It is not uncommon, however, to encounter hearts of normal size with severe degrees of coronary sclerosis.

Coronary sclerosis and peripheral arteriosclerosis are not necessarily concomitant phenomena. Essentially normal coronary arteries are seen at times in cases of marked peripheral arteriosclerosis. Conversely, the coronary vessels may be markedly sclerosed, while there may be little injury to the peripheral vessels.

Knowledge of the etiologic factors in coronary sclerosis is inadequate. It seems fair to consider that coronary sclerosis is a part of the aging process, and the aphorism that "a man is as old as his arteries" might be changed to state that "a man is frequently as old as his coronary arteries." Coronary sclerosis and coronary occlusion are much more likely to develop in men than in women. A person whose family history contains records of severe

vascular disease is predisposed to the development of coronary sclerosis. The ordinary acute infections appear to be unimportant; in fact one is struck by the frequency with which patients who have coronary disease give histories of being remarkably free from episodes of acute infection. Syphilis is a factor in coronary disease in those cases in which syphilitic aortitis produces atresia of the coronary orifices. It is difficult to evaluate the part focal infection plays in the production of disease of the coronary vessels. One gets the impression that patients who have coronary sclerosis have, if anything, less focal infection than the average patient, whereas patients with much focal infection do not seem unduly prone to the development of coronary sclerosis. In my experience, removal of foci of infection in cases of coronary sclerosis has not produced any evident effect on the course of the disease. The occurrence of hypertension accelerates the development of coronary sclerosis, as does diabetes mellitus. Persons with certain constitutional characteristics tend to be victims of coronary sclerosis. Such persons are often powerfully built, and are possessed of great energy and endurance. A life that is strenuous either mentally or physically is frequently the lot of patients who die from disease of the coronary vessels.

The most characteristic symptom of coronary sclerosis is angina pectoris. Heberden's original description¹³ of angina pectoris is exact, and little has been added to it since. Heberden wrote as follows:

"They who are afflicted with it are seized while they are walking (more especially if it be up-hill, and soon after eating) with

a painful and most disagreeable sensation in the breast, which seems as if it would extinguish life if it were to increase or continue, but the moment they stand still all this uneasiness vanishes

"In all other respects the patients are, at the beginning of the disorder perfectly well, and in particular have no shortness of breath, from which it is totally different. The pain is sometimes situated in the upper part, sometimes in the middle, sometimes at the bottom of the os sterni and often more inclined to the left than to the right side. It likewise extends very frequently from the breast to the middle of the arm. The pulse is, at least sometimes, not disturbed by the pain, as I have had opportunities of observing by feeling the pulse during the paroxysm. Males are more liable to this disease, especially such as have passed their fiftieth year. After it has continued for a year or more, it will not cease as instantaneously upon standing still, and it will come on not only when persons are walking, but when they are lying down, especially if they lie on the left side, and oblige them to rise out of their beds. In some inveterate cases it has been brought on by the motion of a horse or carriage and even by swallowing, coughing, going to stool, speaking, or any disturbance of mind.

"Such is the usual appearance of this disease, but some varieties may be met with. Some have been seized while they were standing still or sitting, also upon first waking out of sleep, and the pain sometimes reaches down the right arm as well as the left and even down to the hands, but this is uncommon, in a very few persons the arm has at the same time been numbed and swelled. In one or two persons the pain lasted some hours or even days, but this has happened when the complaint has been of long standing and thoroughly rooted in the constitution, once only, the very first attack continued the whole night."

It is often necessary to make a diagnosis of angina pectoris when cardiac abnormalities are not revealed on general examination or by electrocardio-

graphic or roentgenologic study. It is as if one were called on to identify a man by the shadow he casts or by his silhouette and to do that one must be familiar with every curve, shadow and gesture of the man. To identify a case of angina pectoris without any assistance from any methods of examination demands a most complete mental picture of the syndrome.

I should like to call attention to Heberden's localization of the pain in the sternal region, inasmuch as pains in the lateral portion of the thorax frequently are construed incorrectly as symptoms of disease of the coronary arteries. If pain occurs in the region of the sternum following exertion the presumption is that the case is one of coronary disease, and only the best evidence is sufficient to attribute the pain to any other cause. On the other hand, when the pain is in the left lateral portion of the thoracic wall, the evidence is against a diagnosis of coronary disease and that diagnosis should be made only after the most careful analysis of the symptoms. If the pain is in the left lateral portion of the thoracic wall one must first think of myalgia, intercostal neuritis, herpes zoster, renal colic, diaphragmatic hernia, adherent pericardium, referred pains caused by arthritis of the thoracic portion of the spinal column, lesions of the spinal cord and even the indefinite pains of neurasthenia often associated with cardiac neurosis.

The most characteristic feature of the pain of coronary disease is that it is precipitated by any factor which increases cardiac work and is fairly promptly relieved when the increased demand on the heart ceases. The on-

set of pain following walking is much more convincing in making a diagnosis than it is when it follows the use of the arms, and stooping or bending. The latter exercises bring into play the thoracic muscle, or the spinal column, and lack the value in differential diagnosis of walking, in which many muscles are used. The relation of the pain to changes of weather often identifies it as of rheumatic origin. The details of the manner in which the patient gets relief may be of diagnostic value. One patient, who had his pain in the precordium at night, and who obtained relief by taking warm drinks or by sitting with his back to the fire, proved to have an area of anesthesia in the left lateral portion of the thorax, at the site of his pain, due to advanced hypertrophic arthritis of the thoracic portion of the spinal column.

The brief duration of the pain of coronary disease should be noted. When a patient is subject to repeated attacks of thoracic pain, which last from a half hour to several hours, one must hesitate to make a diagnosis of angina pectoris. A single episode, or at most two episodes, of prolonged precordial pain, may be shown to be associated with one or more attacks of coronary occlusion, but a series of such seizures cannot be so interpreted.

Coronary sclerosis may manifest itself by other symptoms than angina pectoris. Paroxysmal nocturnal dyspnea, with or without pulmonary edema, may be the chief manifestation of coronary sclerosis. However, this symptom is most frequently observed in those cases in which coronary sclerosis is associated with essential hypertension.

Willius and Brown found that in twenty-six per cent of patients with coronary sclerosis, the disease was manifested by progressive myocardial failure, unassociated with seizures of pain. Scott, likewise, has emphasized the fact that there is a considerable group of patients without anginal pain or hypertension, who run the characteristic course of heart failure which proves, at necropsy, to have its basis in coronary sclerosis. As he stated, these patients often are considered to be suffering from chronic myocarditis, which is an erroneous term. This term is doubly unfortunate, indicating that the pathologic process in the heart is inflammatory and implying that "chronic infection elsewhere in the body is responsible for the myocardial damage,"²² for neither of which assumptions is there substantiating clinical or experimental evidence.

And finally, all students of this subject are familiar with the fact that coronary sclerosis, even with coronary occlusion and chronic myocardial infarction, is found in persons who have had no clinical signs of heart disease to the time of their death. This group was designated occult coronary disease by Willius, and comprised forty per cent of his cases.

On general examination there may be no objective evidence of heart disease, and as previously mentioned the diagnosis must rest solely on the interpretation of the patient's symptoms. In a considerable proportion of cases a variable degree of cardiac hypertrophy is present, and this usually occurs with associated hypertension. Significant arrhythmia is relatively uncommon. Pulmonary congestion, and

eventually hepatic enlargement, with edema of the legs, occurs in cases which exhibit the syndrome of chronic heart failure

The roentgenogram of the heart will confirm the presence of hypertrophy when it exists and often reveals calcareous deposits in the aorta. It may also give evidence of widening of the aortic arch, due to torsion and slight ectasia, a finding that is often interpreted erroneously as evidence of aortic aneurysm. Needless to say roentgenographic evidence has only an indirect bearing on the diagnosis of coronary sclerosis.

The greatest confusion exists in the matter of the relation of the electrocardiographic data to the diagnosis of coronary disease. There is a tendency among clinicians to exclude the diagnosis of coronary disease in the absence of significant electrocardiographic changes, and yet Willius³¹ has shown that significant T-wave negativity or abnormalities of the QRS complexes were absent in 63.3 per cent of cases of angina pectoris. As far as my experience goes, coronary sclerosis can affect the electrocardiogram in only three ways. First, a characteristic electrocardiographic change usually is observed in the first two or three weeks following acute coronary occlusion, which in many instances is pathognomonic^{2, 5, 21}. This is followed by inversion of the T-wave and a peculiar RS-T contour described first by Pardee and designated the coronary T-wave by him. The term coronary T-wave is freely and loosely used, and yet this is the only instance that warrants such a designation. The T-wave negativity may require six months to two years

to disappear after infarction. In the second place, coronary sclerosis may affect the function of the auriculoventricular bundle and may lead to varying degrees of heart block. Finally, it may impair conduction in either division of the bundle branches, leading to varying degrees of bundle-branch block with or without inversion of the T-waves. There is yet another condition in which inversion of the T-wave is observed in coronary sclerosis, namely, when that condition is associated with strain, predominantly of one ventricle, usually due to hypertension. Our studies⁴ indicate that this change is primarily due to unilateral ventricular strain rather than to coronary sclerosis. Pardee²⁰ recently described a large Q-wave in lead III of the electrocardiogram, unassociated with right axis deviation, which he considers to be an indication of narrowing of a coronary branch or branches. In sixty-three per cent of the cases studied, this abnormality was not attended by significant changes in the T-wave. If further critical studies confirm this observation, it will become an important electrocardiographic sign indicative of coronary sclerosis.

Finally, it must be emphasized again that by no means is it necessary to have abnormalities of the electrocardiogram before making a diagnosis of coronary sclerosis.

Acute coronary occlusion and myocardial infarction are much more common events than is ordinarily supposed. Studies which Ball and I made of the incidence of myocardial infarction among 1,000 consecutive patients who came to necropsy showed that there was gross myocardial infarction in 49

per cent of hearts In the group of patients in that series who were more than forty years of age, the incidence is 68 per cent Contrary to present ideas, occlusion of the branches of the right coronary artery that go to the left ventricle was found to be common It is no longer justifiable to speak of the anterior descending branch of the left coronary artery as "the artery of coronary occlusion". As a logical sequence to these observations we found infarction of the posterior basal portion of the left ventricle to be practically as common as infarction in the apical and anterior portion of the left ventricle The study further emphasized that myocardial infarction is almost entirely confined to the left ventricle

One cannot enter into a detailed description of the pathologic changes which follow acute coronary occlusion, but certain features are worthy of comment Death may occur following acute coronary occlusion so quickly that an anatomic infarct may not have time to form If one wishes to demonstrate the coronary thrombus in these cases "scissors are unsafe instruments for opening the coronary arteries" because of the danger of dislodging the clot In cases in which infarction has existed a little longer, its presence may be indicated on gross examination only by a region in which muscle softening has taken place and not by changes in the surface coloring of the myocardium Rupture of the heart occurs in the first three weeks, as a rule It is the result of the rapid necrosis of the heart muscle which takes place at that time and not ordinarily the result of cardiac aneurysm, which occurs later, due to thinning of the muscle wall, associated

with more or less complete replacement of the muscle with fibrous tissue. Many infarcts will be overlooked unless the pathologist incises the left ventricle, parallel with and at a distance of 0.5 to 1 cm from the posterior interventricular septum When the muscle beneath a depression in the surface of the left ventricle is sectioned, an underlying chronic infarction often is revealed Mural thrombi are formed frequently when the infarction extends through to the endocardium, or in certain cases of prolonged and severe myocardial failure The danger of a portion of this thrombus becoming dislodged and leading to serious or fatal embolism exists chiefly during the first three weeks after the thrombus is formed Pericarditis occurs in from twelve to fifteen per cent of cases of myocardial infarction, hence the physical signs of this condition may be anticipated in relatively few cases of coronary occlusion Two or more infarcts of varying ages may be found in the left ventricle, and this often explains clinical facts and varying electrocardiographic changes that otherwise might prove puzzling

Acute coronary occlusion frequently afflicts patients not previously subject to symptoms of heart disease Conner and Holt observed that sixty-two per cent of patients with coronary thrombosis did not give histories of antecedent circulatory symptoms Although our experience, and that of Levine, has been that careful questioning usually will disclose a history of angina pectoris or of other symptoms of heart disease, yet the fact remains that acute coronary occlusion is frequently the first intimation of a cardiac disorder

The onset of the attack may be signalized by a severe, prolonged attack of substernal or epigastric pain, occasionally by an attack of severe suffocation, and in rare instances it may occur without pain and with little, if any, dyspnea. The pain is distinguished from the ordinary attack of angina pectoris chiefly by its duration. Often large doses of morphine fail to relieve the patient of pain.

The appearance of the patient following acute coronary occlusion is characteristic in the majority of instances. There is an anxious, grayish facies, and the patient is bathed with perspiration. Dyspnea is usually present. Frequently the patient is nauseated, and severe retching and vomiting are seen in some cases. Fever of one to three degrees develops on the second day and persists for several days. The blood pressure usually falls, sometimes to an alarming degree.

On general examination the apical tones are usually somewhat indistinct, and gallop rhythm is often observed. Pulsus alternans is present occasionally. A friction rub can be heard over the precordium in about twelve to fifteen per cent of cases during the first week. Auricular flutter, auricular fibrillation, or tachycardia of auricular or ventricular origin, is sometimes present. At times the infarct extends high enough in the septum to involve the bundle of His, producing complete auriculoventricular block. Willius⁸⁰ reported two cases in which Stokes-Adams syndrome resulted from such involvement of the auriculoventricular bundle.

Leukocytes number from 10,000 to 20,000 during the first week. A sec-

ondary rise in the leukocyte count may indicate impending myocardial rupture or an additional acute infarction.

The electrocardiographic tracing is characteristically modified, depending on the site of infarction.⁵ When infarction occurs in the anterior portion of the left ventricle and apex, in the region usually supplied by the left coronary artery, the earliest electrocardiographic evidence of the fact is a change of level and contour of the S-T or R-T segment in leads I and II and depression of the S-T interval in lead III. The R-T segment in leads I and II, but especially in lead I, is elevated above the iso-electric line. The segment is likely to be convex, dome-shaped, or sloping downward toward the T-wave. Diphasic T-waves, or T-waves of a monophasic type, are the rule in the earliest stages. It is important to note that leads I and III act conversely, so that elevation of the R-T interval in lead I is opposed by depression of the S-T wave in lead III. The changes in lead II are usually seen to be similar to those in lead I in cases of infarction in the anterior portion of the left ventricle. Two or three weeks after acute coronary occlusion the monophasic or diphasic type of T-wave is replaced by frank inversion. The T-waves are likely to be deep, abrupt, or sharply peaked. It is noteworthy that as the T-wave becomes inverted in lead I, the T-wave in lead III remains upright, and becomes exaggerated and sharply peaked. Of particular significance in this later stage is the rounded contour of the R-T interval in lead I or in leads I and II, preceding inversion of the T-wave. At this stage, the R-T interval is approach-

ing or has reached the iso-electric level.

With infarction in the posterior portion of the left ventricle, alone or combined with apical infarction, precisely the opposite set of conditions is seen. In this case, in the early stages, the R-T segment is elevated in leads II and III and depressed in lead I. The same convex, dome-shaped, or sloping R-T segment preceding the T-wave is apparent in leads II and III. In the later stages, the R-T segment in leads II and III tends to return to and eventually reaches the iso-electric level, and the depressed S-T interval in lead I disappears. In this stage, inversion of the T-wave in leads II and III, with a rounded contour of the preceding S-T segment, is observed, whereas the T-wave in lead I is upright, and becomes exaggerated and more sharply peaked. It must be emphasized that if the patient survives for a period varying from six months to two years, evidence of inversion of the T-wave tends completely to disappear and the electrocardiogram returns to normal.

After the first few days, and for a period of possibly three weeks, portions of the mural thrombus formed over the site of infarction may be dislodged, producing embolism in the systemic arteries. If these emboli lodge in cerebral vessels they are likely to cause death. Death may also occur from rupture of the myocardium due to necrosis extending rapidly through the ventricular wall. A considerable number of patients die from congestive heart failure.

Approximately half of the patients survive acute occlusion of a coronary vessel. Some of these continue to have attacks of dyspnea or anginal pain.

Many have subsequent attacks of coronary occlusion to which they succumb. A considerable proportion of those who survive are free of trouble in six to eighteen months, and are capable of assuming their usual activities with little, if any, reminder that they have been victims of such a vicious cardiac insult.

The problem of coronary sclerosis and occlusion concerns the surgeon in three main ways. First it is obviously important to recognize or to be able to exclude this condition in cases in which operation is to be performed for any cause. Searching interrogation of the patient for a history of anginal seizures, of prolonged attacks of substernal pain or of prolonged seizures of suffocation must always be carried out, especially if the patient is a man of more than forty years of age. Inversion of the T-waves, not associated with cardiovascular conditions that are capable of producing unilateral ventricular strain nor with increased width of the QRS interval of the electrocardiogram often give a clue to the existence of previous coronary occlusion. The peculiar character of these T-waves has been well described by Pardee.¹⁹ Inverted T-waves in leads II and III are commonly indicative of myocardial infarction, particularly if digitalis has not been given. Obviously, an antecedent history of angina pectoris calls for more lively suspicion that infarction has occurred previously.

If it is recognized that acute myocardial infarction has recently occurred, and the patient is in need of a surgical operation, it is advisable to postpone operation, if possible for three months, for the studies of White

have shown that healing is fairly complete in that length of time. Of course, operation may be undertaken then only if examination demonstrates that cardiac compensation is satisfactory. Under certain urgent conditions it has been found possible successfully to perform a major operation on patients whose acute coronary occlusion occurred as recently as two weeks prior to the operation. However, this is permissible only in emergencies, or in cases in which attacks have been mild, have been accompanied by a minimal amount of shock, and in which there is no evidence of heart failure after the attacks.

The surgeon, and the internist as well, are vitally interested in distinguishing acute coronary occlusion from pathologic conditions in the abdomen, particularly cholelithiasis, perforating peptic ulcer, intestinal obstruction, and acute pancreatitis. This difficulty comes about because acute coronary occlusion may register its pain in the abdomen, whereas, the abdominal lesions enumerated may produce pain in the lower part of the thorax with radiation of pain to the shoulders and even at times to the arms. As Tuohy remarked, collateral and associated evidence is often of more importance than direct evidence and symptoms in arriving at the correct diagnosis. Although the differential diagnosis cannot always be made, yet vivid appreciation that coronary thrombosis can simulate the abdominal conditions named will avoid many embarrassing surgical experiences.

First and foremost, one must be ever mindful of the menace of coronary occlusion among patients who are more

than forty years of age, and particularly if the patient is a male. An antecedent history of angina pectoris or paroxysmal nocturnal dyspnea speaks strongly for the possibility of acute epigastric pain having its basis in acute coronary obstruction. The absence of such a history does not allow one to exclude from consideration acute coronary occlusion, however. The presence of essential hypertension, or its preexistence, predisposes to an attack of coronary occlusion.

The most important step in distinguishing acute conditions in the abdomen from acute coronary obstruction, is the careful taking of the anamnesis. This is particularly true if patients have cholelithiasis or peptic ulcer, in such cases a painstaking review of the history usually will suffice to establish the presence of these conditions. If one remembers that cardiac arrhythmia, muffled apical heart tones, gallop rhythm, friction rub and particularly a rapid drop in blood pressure are symptoms of cardiac insult, the differential diagnosis usually can be made. Wilkus and Fitzpatrick found that the gallbladder was diseased in twenty-four per cent of cases of coronary sclerosis. When disease of the gallbladder or peptic ulcer exists with acute coronary obstruction, it may be difficult or impossible to arrive at a differential diagnosis.

It can now be said that the electrocardiogram assumes the greatest importance in the differential diagnosis of these conditions. Abnormalities of the electrocardiogram which have been enumerated, appear as early as four hours after acute myocardial infarction, and may retain a highly characteristic

appearance for two to three weeks or longer. It is imperative, therefore, for the internist and surgeon to familiarize themselves with these highly diagnostic changes.

In distinguishing acute coronary obstruction from acute pancreatitis and intestinal obstruction, the electrocardiogram may be of diagnostic value if twenty-four or more hours have elapsed after the onset of the attack. The fecal vomiting, "ladder pattern" seen on inspection of the abdomen, and abdominal rigidity will establish the diagnosis of intestinal obstruction as a rule. As between acute pancreatitis and coronary disease the diagnosis must rest on the occurrence of local tenderness and rigidity in pancreatitis, the history relative to coronary disease, the physical signs of cardiac injury, and possibly on the electrocardiographic changes.

Finally, the surgeon is interested in

the problem of the surgical treatment of angina pectoris. Here a plea for conservatism must be made. First of all, operations undertaken on patients with angina pectoris are done at considerable risk. Second, if the surgeon is successful in alleviating pain there is no reliable evidence to indicate that he has modified the serious pathologic process that is the basis for the pain. It is even debatable how much one is justified in depriving the patient of the signal which will warn him that his heart is in distress. At present we are inclined to reserve attempts at surgical relief to patients who fail to obtain reasonable help from the combined use of xanthine derivatives and adherence to a strict regimen. If this treatment fails, the surgical procedure of choice is the conservative method, consisting of paravertebral injection with alcohol of the upper five thoracic nerves.

REFERENCES

- ¹ANREP, G. V., and SEGALL, H. N. The regulation of the coronary circulation, *Heart*, 1926, XIII, 239-260.
- ²BARNES, A. R. Electrocardiographic localization of myocardial infarcts, *Med Clin N Am*, 1930, XIV, 671-686.
- ³BARNES, A. R., and BALL, R. G. The incidence and situation of myocardial infarction in 1,000 consecutive post-mortem examinations, *Proc Staff Meetings Mayo Clin*, 1930, v, 367-359.
- ⁴BARNES, A. R., and WHITTEN, M. B. Study of T-wave negativity in predominant ventricular strain, *Am Heart Jr*, 1929, v, 14-67.
- ⁵BARNES, A. R., and WHITTEN, M. B. Study of the R-T interval in myocardial infarction, *Am Heart Jr*, 1929, v, 142-171.
- ⁶BARNES, A. R., and WILLIUS, F. A. Cardiac pain in paroxysmal tachycardia, *Am Heart Jr*, 1927, II, 490-496.
- ⁷BENSON, R. L. The present status of coronary arterial disease, *Arch Path and Lab Med*, 1925, II, 876-916.
- ⁸CAMPBELL, J. S. Stereoscopic radiography of the coronary system, *Quart Jr Med*, 1929, XXII, 247-267.
- ⁹CONNOR, L. A., and HOLT, EVELYN. The subsequent course and prognosis in coronary thrombosis, An analysis of 287 cases, *Am Heart Jr*, 1930, v, 705-719.
- ¹⁰EAST, C. F. T., and BAIN, C. W. C. Recent advances in cardiology, 1929, P. Blakiston's Son and Co., Philadelphia.
- ¹¹GROSS, LOUIS. The blood supply to the heart in its anatomical and clinical aspects, 1921, Paul B Hoeber, New York.
- ¹²HAINES, S. F., and KEPLER, E. J. Angina pectoris associated with exophthalmic goiter and hyperfunctioning adenomatous goiter, *Med Clin N Am*, 1930, XIII, 1317-1324.
- ¹³HERBERDEN, W. Some account of a dis-

- order of the breast, Med Tr College of Phys, London, 1772, II, 59
- ¹⁴KEERER, C S, and RESNIK, W H Angina pectoris a syndrome caused by anoxemia of the myocardium, Arch Int Med, 1928, **XL**, 769-807
 - ¹⁵KERNOHAN, J W Personal communication to the author
 - ¹⁶LEVINE, S A Coronary thrombosis its various clinical features Medicine, 1929, **VIII**, 245-418
 - ¹⁷METTIER, S R, ZSCHIESCHE, LOUISE J, and WEARN, J T Demonstration of direct vascular communications between the coronary arteries and chambers of the heart, Tr Assoc Am Phys, 1929, **XLV**, 345-347
 - ¹⁸OBERHILTMAN, H A, and LECOUNT, E R Variations in anastomosis of the coronary arteries and their sequences, Jr Am Med Assoc, 1924, **LXXXII**, 1321-1325
 - ¹⁹PARDEE, H E B Heart disease and abnormal electrocardiograms, with special reference to the coronary T-wave, Am Jr Med Sci, 1925, **CLXX**, 270-283
 - ²⁰PARDEE, H E B The significance of an electrocardiogram with a large Q in lead 3, Arch Int Med, 1930, **XLVI**, 470-481
 - ²¹PARKINSON, JOHN, and BEDFORD, D E Successive changes in the electrocardiogram after cardiac infarction, Heart, 1928, **XV**, 195-239
 - ²²SCOTT, R W Clinical and pathological aspects of coronary disease, Ohio State Med Jr, 1929, **XLV**, 349-354
 - ²³SPALTEHOLZ, WERNER Die Arterien der Herzwand, 1924, S Hirzel, Leipzig
 - ²⁴TUOHY, E L Discussion, Jr Am Med Assoc, 1928, **XCI**, 1521-1523
 - ²⁵WALMSLEY, THOMAS The heart In Quan's Elements of anatomy, 1929, vol 4, pt 3, 152 pp Longmans, Green and Co, London
 - ²⁶WEARN, J T The rôle of the thebesian vessels in the circulation of the heart, Jr Exper Med, 1928, **XLVII**, 293-316
 - ²⁷WHITE, J H The healing of myocardial infarction (Unpublished data)
 - ²⁸WHITTEN, M B The relation of the distribution and structure of the coronary arteries to myocardial infarction, Arch Int Med, 1930, **XLV**, 383-400
 - ²⁹WILLIUS, F A Angina pectoris An electrocardiographic study, Arch Int Med, 1921, **XXVII**, 192-223
 - ³⁰WILLIUS, F A Infarction of the interventricular septum with complete heart-block and Stokes-Adams' seizures, Med Clin N Am, 1926, **x**, 601-604
 - ³¹WILLIUS, F A, and BROWN, G E Coronary sclerosis an analysis of eighty-six necropsies, Am Jr Med Sci, 1924, **CLXXIII**, 165-180
 - ³²WILLIUS, F A, and FITZPATRICK, JULIA M The relationship of chronic infection of the gall-bladder to disease of the cardiovascular system, Jr Iowa State Med Soc, 1925, **xv**, 589-592
 - ³³WILLIUS, F A, and GIFFIN, H Z The anginal syndrome in pernicious anemia, Am Jr Med Sci, 1927, **CLXXIV**, 30-33

Pulmonary Infections by the Friedländer's Bacillus (*Bacillus Mucosus Capsulatus*)*†

BY FRANK FREMMEL, M D., KARL J. HENRICHSEN, M D., AND
HENRY C. SWEANY, M D., *Chicago, Ill*

SINCE Weichselbaum's¹ work in 1886, it has been known that the micro-organism described by Friedlander² in 1882-3, can cause pulmonary disease *suu genenis* Friedlander's conception, however, that it was the cause of all pneumonias, was disproved by Frankel just prior to Weichselbaum's report. On the other hand, Frankel considered the micro-organism only a secondary invader and not the primary cause of any pneumonia—a conception that was also partially erroneous, and one that divided medical opinion for many years.

Sisson and Thompson³ emphasized this and pointed out that Osler as late as 1912 expressed Frankel's view in his text book on medicine. Gradually, however, reports have accumulated to show the true status of the parasite, viz that from one to eight per cent of pneumonias are caused by it. The work of Weichselbaum has, therefore, been confirmed by a large number of authors, the most important of whom are Étienne,⁴ 1895, Comba,⁵ 1896, Smith,⁶ 1897, Thiroloux,⁷ 1897, Howard,⁸ 1898, Bero,⁹ 1899, Moiseyeff,¹⁰ 1900, Brinckerhoff and Thompson,¹¹

1901, Kakawa,¹² 1904; Stuhlern,¹³ 1904, Apelt,¹⁴ 1908; Brissaud,¹⁵ 1912; Gouget and Moreau¹⁶ 1912; Mosny and Pruvost,¹⁷ 1913, and Zander,¹⁸ 1928.

Some of the authors tend to dissociate these infections from other lung infections and to establish them as separate disease entities. Especially is this true of the chronic form.

The unusual features of these infections are a definite and specific bacteriology, a peculiar clinical course with sudden death and extremely high mortality, and a characteristic gross and microscopic pathology.

The clinical course of the disease is not always regular, but most authors speak of a sudden onset, usually without a chill, no herpes labialis, death coming suddenly between two to five days, usually before the third day. Occasionally, however, the process may resemble closely a lobar pneumonia except that it usually terminates more suddenly. The physical findings are given by Weill and associates¹⁹ as those of engorgement rather than hepatization, even in the advanced process. There are signs of some dullness, with suppression of breath sounds, and an absence of subcrepitant râles. This is perhaps due to the large numbers of

*Received for publication, May 4, 1931.

†From the Research Laboratories of the Municipal Tuberculosis Sanitarium, Chicago.

encapsulated bacilli that fill the alveoli and finer bronchi with a sticky mucoid material, preventing the passage of air.

The mortality figures differ slightly, but with the exception of Zander¹⁸ who reported an epidemic of the disease where the mortality was thirty-five per cent, the mortality figures are high. Netter, quoted by Étienne,⁴ Brissaud,¹⁵ Mosny and Pruvost,¹⁷ Gouget and Moreau,¹⁰ Kakawa,¹² and others, stated that the disease is nearly always fatal. Lord,²⁰ in 1915, said that no authentic case had ever recovered. There are sporadic reports, however, of patients of varying grades of chronicity. Recently Belk,²¹ Westermarck,²² Collins and Kornblum²³ and others have reported such cases.

Zander's series, mentioned above, seems to be unusual in that it assumed epidemic proportions, yet had a much lower mortality than is reported for the sporadic cases, and perhaps is more truly representative because it is a series nearly as large as all others reported, put together. It shows the effect of such an infection on an average group of people (soldiers in a prison camp), while Friedländer's infection is usually reported as occurring, most frequently in people of low vitality, quite commonly in alcoholics around fifty years of age. It is possible that many recoveries are never reported or even suspected as such infections.

The roentgenologic findings are rather meager. Weill thought that it differs from pneumonia in having a less tendency to show triangles, and Collins and Kornblum,²³ in being less dense, more scattered and nearer the periphery of the lung in location.

The bacteriology is relatively con-

stant. The causal organism is a large round ended, gram negative, heavily encapsulated bacillus. It has since been placed in a distinct group of encapsulated micro-organisms. Although it resembles the organisms found in rhinoscleroma and ozena, and also other members of the group, it is quite different in pathogenicity. Culturally, it resembles the colon-aerogenes group, but differs in its heavy capsules and in a few incidental reactions. Some authors suggest an origin from this group, but such ideas have not met with general acceptance. Notwithstanding the fact that strains of these micro-organisms have a general similarity, there are slight variations that may very well account for some of the clinical and pathological differences.

The pathological changes are the most distinctive and will, when taken together with other findings, differentiate this condition from other lung affections. Moiseyeff,¹⁰ Kakawa¹² and Brissaud¹⁵ emphasized its individuality. While Sisson and Thompson³ stated that no feature is pathognomic, yet when all are taken together it is quite easy to make a diagnosis. The most important pathologic findings are the pseudolobar consolidation due to a dense confluence of bronchopneumonic foci (rarely true lobar), the absence of a red stage of hepatization, the presence of a mucoid exudate on the cut surface giving it a glazed appearance, the scarcity and irregularity of red cells and fibrin within the alveoli, and the presence of a moderate number of monocytes containing large numbers of the encapsulated bacilli. Hyperemia and thrombosis of the alveolar vessels lead up to a necrosis and ab-

DISCUSSION

One of the striking features of this case was the rapid evolution and apparent utter hopelessness of treatment. This is in harmony with the majority of reports. Although the cases reported by Zander¹⁸ and the scattering ones in which the disease becomes chronic, will be encouragement for further effort, there appears to be some unknown toxic

substance that overwhelms the patient. This assumption is well supported because only the left lower lobe was involved, yet a profound agranulocytosis of the blood developed, with collapse and death within twenty-six hours from the initial chill. It seems reasonable to suppose that a soluble toxin may be responsible for the sudden prostration. If such should be found, there

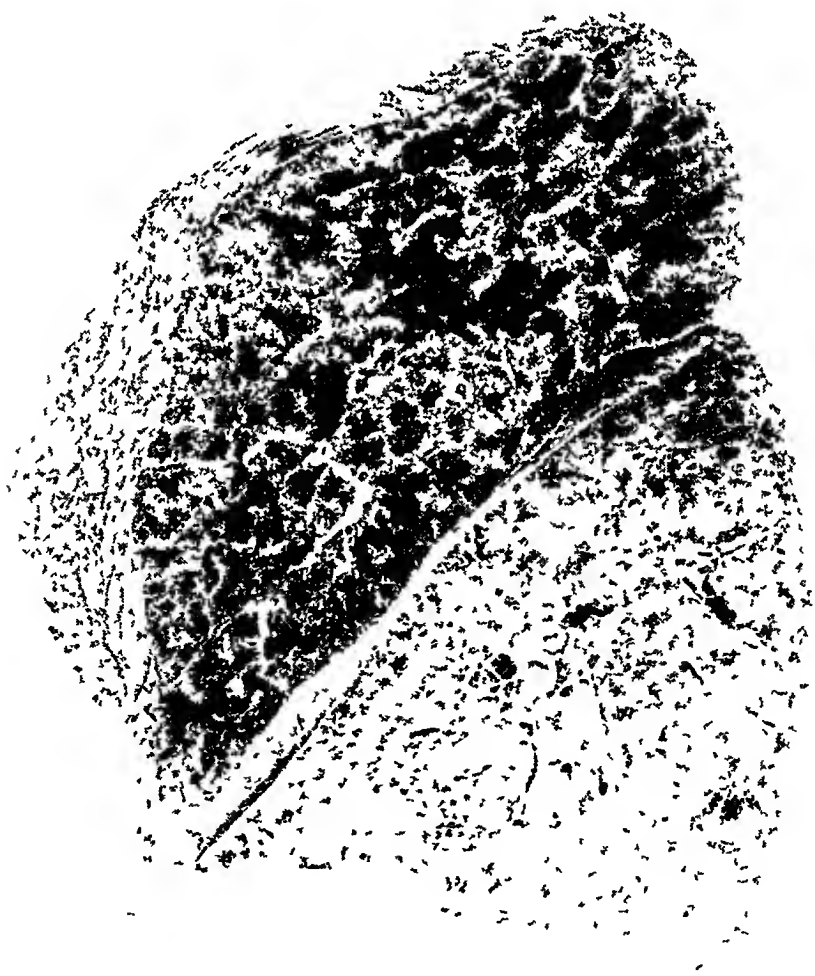


FIG 1 Antero-posterior sagittal section through the middle of the left lung. Huge pneumonic focus in the middle of the lower lobe, extending out to the pleura except at the extreme margins. While this is almost lobar in extent, it is essentially the same type of lesion that begins as a smaller focus.

is no disease in which there is greater need for an antiserum so far as the individual patient is concerned

Perhaps the greatest need in these infections is promptness in diagnosis. This dictum is true of any disease but, here, from a prognostic standpoint it is especially valuable. The diagnosis

can be made only by finding the encapsulated bacilli inside of monocytes in the sputum, the cellular content of which is predominantly monocytic. This, with vague physical signs of pulmonary engorgement, accompanied by a cyanosis and physical state out of proportion to the physical and x-ray

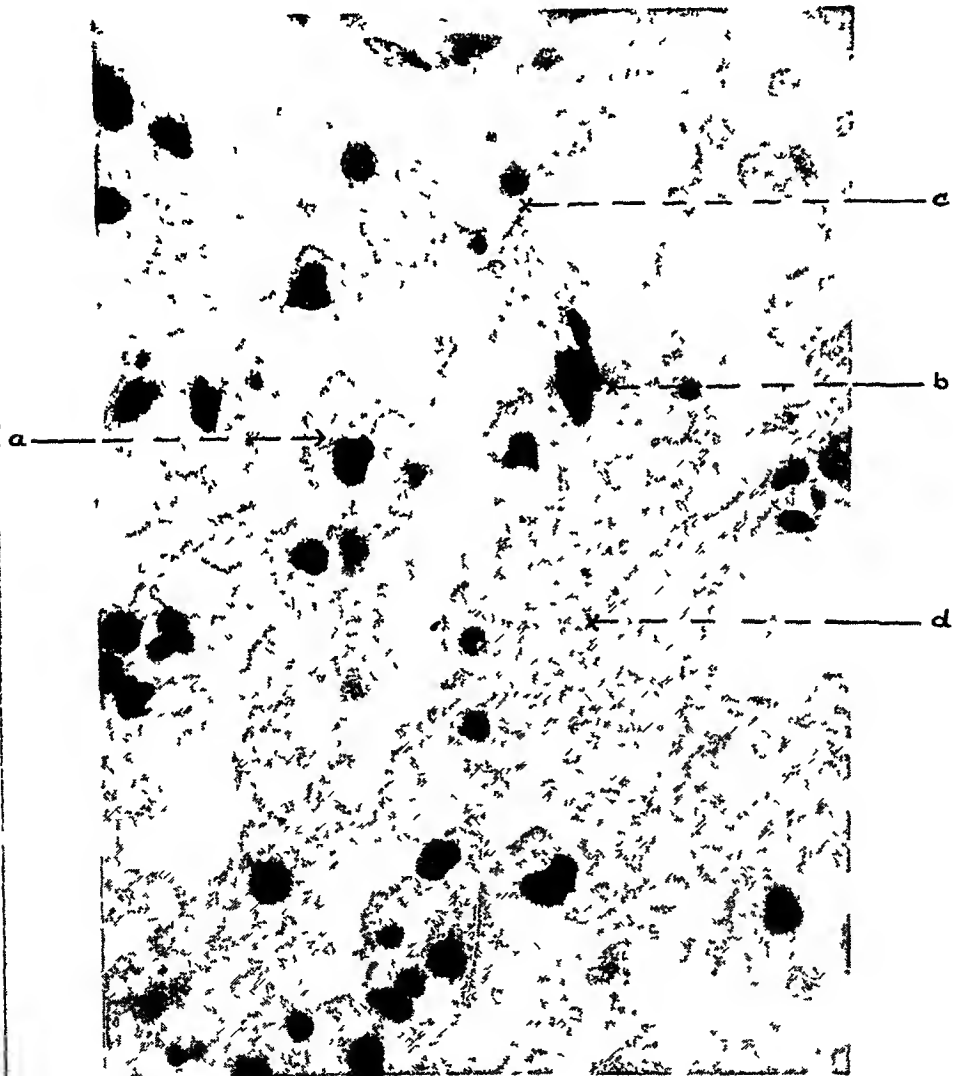


FIG 2 High power photomicrograph of the pneumonic process, showing a monocyte (a) containing encapsulated bacilli, alveolar wall (b) with necrosis and rupture at 'c' and 'd' X1090

findings, establishes the diagnosis. Subsequently, the x-ray shadows become more pronounced (but never like a lobar pneumonia). Bacilli may be found in the blood. It must be differentiated from croupous, broncho-, and (rarely) lobar pneumonia. Although our acute case was a lobar pneumonia, few authors report typical lobar types. Most of them (Brissaud,¹⁵ Kakawa,¹² Moiseyeff,¹⁰ Étienne,⁴ and others) consider the most common type a "pseudo-lobar" or irregularly confluent bronchopneumonia with a less common true bronchopneumonia. Only a few (Brissaud and Kakawa) make mention of a true lobar pneumonia. The differentiation from these conditions must be based on the sputum findings together with the vague and almost negligible physical signs (râles in particular) in an extremely ill patient. The explanation of the paucity of râles is no doubt found in the extreme viscosity of the exudate. This, in turn, is due to the mucoid capsules of the bacilli.

As to the chronic types, they must be differentiated from pulmonary abscesses and gangrene, unresolved pneumonias, particularly that of influenza, and pulmonary tuberculosis. From the common abscess it may be differentiated by the characteristic sputum with the bacilli and the relatively slight odor. From influenza by the sputum with the characteristic bacilli, and from tuberculosis on the bacteriological findings and, according to Kornblum,²³ by the thin walls of the cavities as shown on the x-ray. Our chronic case was indistinguishable, however, from some types of ulcerative pulmonary tuberculosis.

SUMMARY

An extremely acute type of Friedlander's bacillus infection is reported, the patient living only twenty-six hours from onset to death. The clinical findings corresponded to those usually reported for the disease. The pathological findings were those of an uncommon lobar pneumonia instead of a confluent bronchopneumonia, or a "pseudo" lobar pneumonia. The disease began by a rapid growth of the encapsulated micro-organisms in the alveoli and smaller bronchi, causing an exudate rich in edema fluid containing scattering monocytes, irregularly placed fibrin, with an occasional hemorrhage into the alveoli. This aspect has only a gray to yellow-gray appearance grossly, and accounts for the infrequent appearance of the red stage of hepatization. Death occurred before the other stages could develop. Ordinarily the evolution of the lesion from the "red" stage is characterized by an infiltration of polymorphs along the alveolar walls, forming in crescents along the plugs composed of bacilli, monocytes, and varying amounts of fibrin. Later an invasion of the alveolar wall results in a huge dilatation of the alveolar capillaries, followed by thrombosis, necrosis, and abscess formation. The last two processes correspond to the stage of resolution of pneumococcus pneumonia. The dilatation of the alveolar capillaries, with an occasional rupture into the alveoli, give to the lesions a mottled dark red appearance that is occasionally present.

If the patient survives this stage, a gradual change to a chronic form ensues, with a substitution of lymphocytes and plasma cells for the poly-

morphs and an invasion of the older lesions with fibroblasts, connective tissue, and a true metaplasia forming squamous or cuboidal epithelial cells over the cavity walls. When the disease is progressive, there is a continuous sequence of lesions that begins in small bronchopneumonic foci and

passes through the various stages of evolution described above, usually extending downward towards the base until death.

The bacteriologic studies included in this report have been made by Miss Asya Stadnichenko, for which we wish to express our gratitude.

REFERENCES

- ¹WEICHELBAUM, A. Über die Aetiologie der acuten Lungen- und Rippenfellentzündungen, *Med Jahrb*, 1886, I, 483-554.
- ²FRIEDLÄNDER, C. Über die Schizomyceten bei der acuten fibrosen Pneumonie, *Virchows Arch f path Anat*, 1882, LXXXII, 319-324.
Die Mikrokokken der Pneumonie, *Fortschr d Med*, 1883, I, 715.
- ³SISSON, W R, and THOMPSON, C B. Friedlander bacillus pneumonia, with report of cases, *Am Jr Med Sci*, 1915, cl, 713-727.
- ⁴ÉTIENNE, G. Le pneumo-bacille de Friedlander, son rôle en pathologie, *Arch de med expér et d'anat path*, 1895, VII, 124-157.
- ⁵COMBA, C. Abstract *Jahrb u d Fortschr d path Mikroorg*, 1896, XII, 101. From uno caso di setticemia da bacillo del Friedlaender in un neonato associata a sclerema, *Sperimentale*, II, 2p, 112.
- ⁶SMITH, W H. A case of lobular pneumonia due to the bacillus mucosus capsulatus or bacillus of Friedlander, *Bost Soc Med Sci*, 1897-98, II, 174-179.
- ⁷THIROLOIX. Pneumonie due au bacille de Friedlander, *Bull Soc anat de Paris*, 1897, LXXII, 152-154.
- ⁸HOWARD, W T. The importance of the bacillus mucosus capsulatus (b of Friedlander) as the cause of acute and chronic infections, *Phil Med Jr*, 1898, I, 336-338.
- ⁹BECO, L. Recherches sur la fréquence des septicémies secondaires au cours des infections pulmonaires, *Rev de med*, 1899, XIX, 461-479.
- ¹⁰MOISEYEFF, A I. K pathologicheskoi anatomii i histologii Friedlander ovskoi pneimonii (Pathological anatomy of Friedlander's pneumonia), *Bolnitsch gaz Botkina*, 1900, XI, 889-996.
- ¹¹BRINCKERHOFF, W R. Report of a case of acute lobar pneumonia due to the bacillus mucosus capsulatus, *Med and Surg Rep Bost City Hosp*, 1901, XII, 149-158.
- ¹²KAKAWA, I. Zur pathologischen Anatomie der Kapselbazillen - Pneumonie (nebst Anhang über Kapselbazillen-Meningitis), *Deutsch Arch f klin Med*, 1904, LXXX, 39-74.
- ¹³STUHLERN, V R. Über die Bedeutung des Bacillus pneumoniae Friedlander als Erreger von Pneumonie, *Centralbl f Bakteriöl*, 1904, XXXVI, 493-505.
- ¹⁴APELT, F. Über die durch den Bazillus pneumoniae Friedlander hervorgerufene Pneumonie, *Munch med Wchnschr*, 1908, LV, 833-837.
- ¹⁵BRISSAUD, H. Le pneumobacille de Friedlander, recherches personnelles, etat actuel de la question, 1912, *Lyon med LXXXIII*, 205.
- ¹⁶GOUGET, A., et MOREAU, R. Pneumonie lobaire a pneumobacilles, *Bull et mem Soc med d hop de Paris*, 1912, XXXIV, 296-304.
- ¹⁷MOSNY, M M, et PRUVOST, P. Un cas de pneumonie a pneumobacille de Friedlander avec septicémie, *Bull et mem Soc med d hôp de Paris*, 1913, XXXV, 395-401.
- ¹⁸ZANDER. Ausgedehnte Endemie von Lungentzündungen durch Infektion mit Friedländerschen Pneumobazillen unter Zuhilfenahme, *Deutsch med Wchnschr*, 1919, XLV, 1180.
- ¹⁹WEILL, M M, MOURIQUAND, DUFOURT,

- et BLAND-PERDUCET Pneumonie à pneumobacille de Friedlander considérations radioscopiques et cliniques, Lyon méd, 1914, CXXII, 133-136
- ²⁰LORD, F T Diseases of bronchi, lungs and pleura, 1915, Lea and Febiger, Philadelphia, p 234
- ²¹BELK, W P Pulmonary infections by Friedlander's bacillus, Jr Infect. Dis, 1926, XXXVIII, 115-126
- ²²WESTERMARK, N Ein Tuberkulose vortauschender Fall von Friedlander's Pneumonie mit lange sich hinziehendem Verlauf, Acta radiol, 1926, VII, 626-631
- ²³COLLINS, L H JR, and KORNBLUM, K Chronic pulmonary infection due to Friedlander bacillus, clinical and roentgenologic study, Arch Int Med, 1929, XLIII, 351-362
- ²⁴SWEANY, H C, STADNICHENKO, A, and HENRICHSEN, K L Multiple pulmonary abscesses simulating tuberculosis caused by Friedlander bacillus, Arch Int Med, 1931, XLVII, 565-582

The Phobia of High Blood Pressure

“**A**T present, the general public, at least in the large cities, is entirely too well acquainted for its own good with the dangers of arterial hypertension. Almost everyone knows some unfortunate who had high blood pressure and died suddenly in the street, or is now paralyzed in half his body. Or when he tells his solicitous friends that he has been discovered to have high blood pressure, they will fill in the gaps in his knowledge of the dangers of the disease. Fortunately, by now the blood pressure has been measured long enough for one to have communicative friends who have had the dreaded high blood pressure for many years and ‘never been hurt by it’. It is very common nowadays for one who has always felt well to learn as a result of an insurance or periodic examination or a visit to the doctor for some trivial complaint that he or she has high blood pressure. Then, often enough, the peace of mind of the patient is gone, symptoms make their appearance, and there start the troubles of the patient and, even more, of the family

At the outset, it is to be emphasized that *many individuals with essential hypertension not only need no treatment whatsoever, but are much better off without it*. Many persons with asymptomatic hypertension would have been more fortunate if they had never learned of their hypertension”—(From *Hypertension and Nephritis* by ARTHUR M FISHBERG Second Edition, 1931 Lea and Febiger, Philadelphia)

Syphilis of the Lung*†

Report of a Case with Autopsy Findings

BY HAROLD COMONFORT DENMAN, M D , F A C P , *Brooklyn, N Y*

FLOCKEMANN,¹ whose comprehensive review of the literature of pulmonary syphilis was published in 1898, stated that "the existence of pulmonary syphilis in the adult has not been proved to be very probable" This statement has been doubted by other writers on the subject Rossle² believed that the frequency of pulmonary lues in the adult is underestimated and reported twenty-five cases which he himself had observed Allison³ stated that "Syphilis of the lung in the adult is unquestionably rarely encountered However it is not so rare as pathologists would lead us to believe, and conversely, not nearly so common as some clinicians and roentgenologists seem to think" This uncertainty, the difficulty of diagnosis and the paucity of characteristic findings in pulmonary syphilis have prompted the report of the following case

W G , a laborer, aged 42 years, was admitted to the medical service of Kings County Hospital, November 9, 1930, because of a hemorrhage from the mouth The following history was obtained from the patient Two months before admission, he had noticed a persistent cough productive of a small amount of sputum This cough was never

excessive nor painful The sputum was in small amount, white and never blood tinged He noticed also a slight but increasing weakness during this period, which did not interfere with his usual work The hemorrhage which was the cause of his admission to the hospital, occurred suddenly, without cough, pain or unusual exertion, and was described by the patient as a gush into the mouth of blood, bright red in color and slightly frothy He was unable to state the amount Associated symptoms were lacking, there were no chills, fever, no sweats, dyspnea, palpitation or precordial pain He had a fair appetite, no nausea, no vomiting, bowels regular, not medicated He slept well, and suffered no discomfort from a nocturia, twice nightly, except the inconvenience, and although poorly nourished, had noticed no appreciable recent loss of weight

The *family history* shows that his father died of erysipelas, age not known to the patient His mother, two sisters and one brother are alive and well, no history of tuberculosis, malignancy or congenital disease is present

Previous personal history During childhood the patient had measles During adult life the only disease was acute rheumatic fever at the age of 23 years While serving in the World War he was informed that he had heart disease, but was not discharged for incapacity His habits were regular, drinking very little alcohol, no coffee, tea freely, but not to excess

Physical examination revealed a slight, small framed, poorly nourished, pale, adult male about five feet five inches tall, complaining of weakness and a recent hemorrhage from the mouth Head, eyes, nose,

*Received for publication, April 10, 1931

†From the Medical Service, Kings County Hospital, Brooklyn, N Y

and ears were negative. There were no glandular enlargements in the neck or axilla. Chest examination showed a narrow, asthenic type, with markedly diminished expansion of the entire left side. Tactile fremitus was present anteriorly, to a less extent below the third rib, than over the corresponding area on the right side. This tactile fremitus was increased in the left axilla and absent over the left base posteriorly below the fifth dorsal spine and laterally to the scapula angle. The supra- and infraclavicular fossae were deeper on the left side. There was no dilatation of the superficial veins of the chest. Percussion revealed the presence of a solid body in the third left interspace between the mid-clavicular line and the sternum. Between the mid-clavicular line and the mid-axillary line from the third to the seventh interspaces a hyperresonant note was present. Flatness was present posteriorly below the level of the fifth dorsal spine and laterally to the scapular angle. On auscultation the breath sounds were diminished anteriorly and in the axilla, and increased at the level of the third space anteriorly with occasional loud "bubbling" râles over this area, and absent over the flat base posteriorly. The voice sounds were diminished slightly anteriorly and not transmitted at the base posteriorly. There were fine crepitant râles over the left apex only after an expiratory cough, none at the base. The right side gave the physical signs of compensatory breathing.

The cardiac apex impulse was visible and palpable 8 cm from the mid-line in the fifth interspace, the rate was 100, normal sinus rhythm. There were noticeable carotid and subclavian pulsations. The left border was percussed 8.5 cm in the fifth interspace, the right border, 4 cm to the right in the fourth interspace, and the arch, 6.5 cm at the level of the second interspace. The first cardiac sound was entirely replaced at the apex and base by a harsh systolic murmur, followed by a short, ringing, greatly accentuated second sound. The radial pulses were equal and regular. The abdomen showed no localized areas of tenderness, no palpable masses and no herniae. The inguinal glands were palpable and hard. Rectal examination revealed a normal pros-

tate. The extremities were negative, and reflexes normal. The blood pressure in the right arm was 110/60, in the left, 114/70.

The possibilities in this patient were abscess of the lung, aneurysm of the aorta, tuberculosis, gumma of the lung, malignancy. Although there was a slight effusion in the left pleural cavity on admission, it was believed to be due to, rather than the cause of, the localized findings (Figure 1). Seventeen days after admission the patient showed signs of a rapidly formed, large effusion in the left pleural cavity and a roentgen picture at this time proved the presence of an effusion, which on aspiration was bloody (Figure 2).

During the patient's stay in the hospital, his main complaint was an increasing weakness, with a slight unproductive cough. Although his lesion changed, his complaint remained much the same, weakness. On admission his temperature was 100° going to normal in two days and remittent thereafter, varying between 99.6° and 102°, the average being 99.9°. The pulse rose to 120, the respirations to 34, averaging 26. After withdrawing 1,000 cc of sero-sanguineous fluid from the left pleural cavity on the seventeenth day, for an artificial pneumothorax, a thoracentesis was necessitated again on the thirty-fifth day with the withdrawal of 2,000 cc of bloody fluid, but without great relief. An increasing dyspnea and cyanosis supervened. His pulse became weak and more rapid, his right chest gave evidence of a beginning passive congestion, hemoptysis recurred with the loss of four ounces of bright red blood, and on the forty-ninth day of hospitalization, the patient expired. The laboratory reports gave normal urine, sputum negative for tubercle bacilli on fourteen occasions, blood Wassermann four plus, blood chemistry normal. The blood count and differential was white blood cells, 10,800, red blood cells, 4,200,000, polymorphonuclears, 78 per cent. In the examination of the pleural fluid cancer cells were not observed. Guinea pig inoculation was negative for tuberculosis.

A post mortem examination was performed by Dr. William W. Hala, director of the pathological laboratories of the Kings Coun-

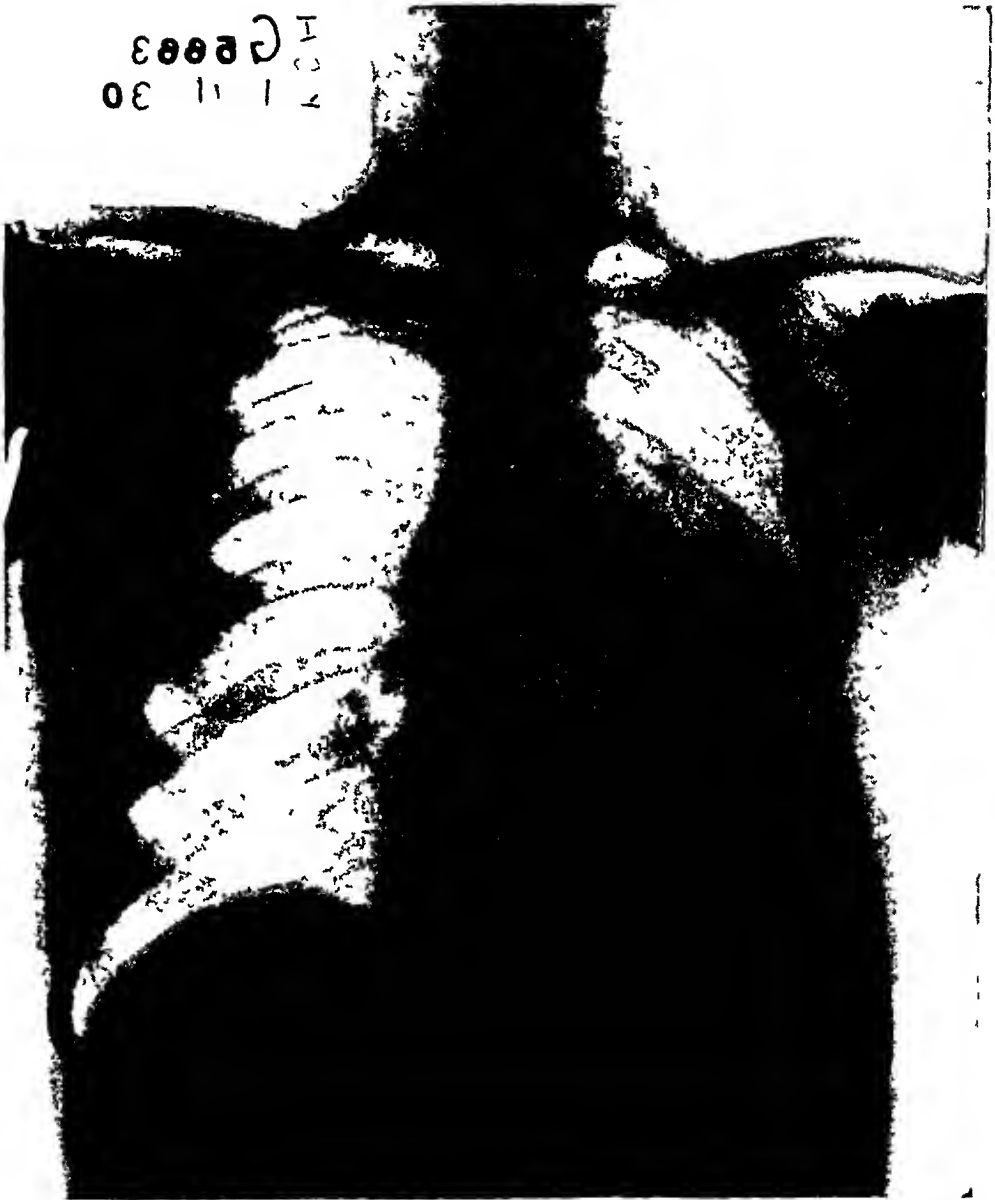


FIG 1 (Nov 13, 1930) Absent aeration of the left lower lobe. Small effusion in the costo-phrenic space. Left chest smaller than the right. Moderate compensatory emphysema of the right lung. The left border of the heart shadow obscured by lung pathology. (Interpretation of the x-ray films was by Dr Richard A. Rendich, roentgenologist at Kings County Hospital.)



FIG 2 (Dec 1, 1930) Complete absence of illumination of the left lung field, consequent to a large collection of fluid in the pleural cavity, slight displacement of the heart and mediastinal contents to the right



FIG 3 (Dec 1, 1930) Oblique view after removal of one liter of sero-sanguineous fluid, air injection for study of pleural neoplasm—latter excluded by the normal pleural contour. Saccular aneurysm of the descending aorta now distinctly visualized. (From a P A view at the same time, the patient lying on his right side, the horizontal level of the remaining fluid was noted, with the absence of neoplastic mass of the parietal pleura)

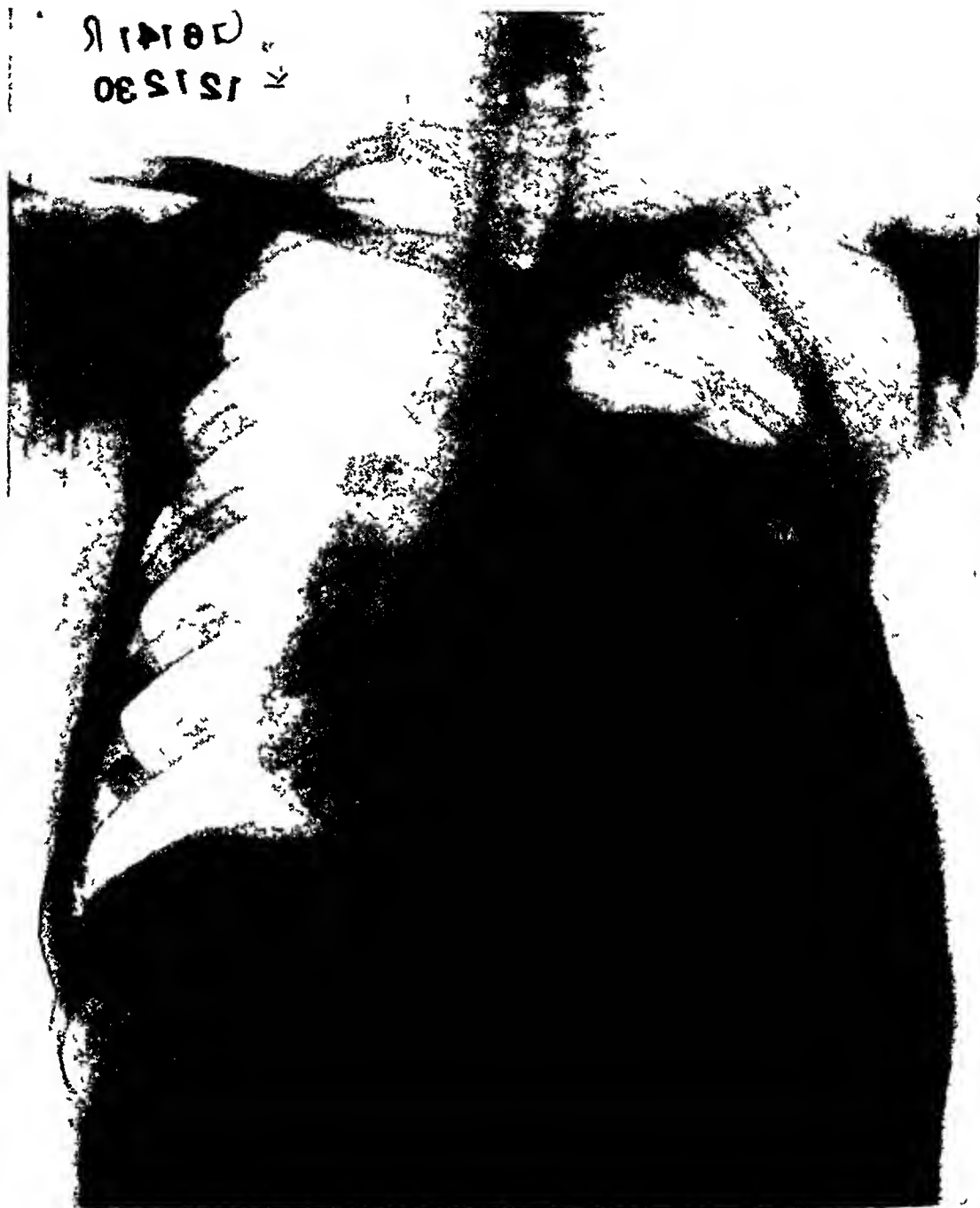


FIG 4 (Dec 12, 1930) Further accumulation of fluid—several levels denoting small encysted collections

ty Hospital, whose report follows, only data of positive interest being recorded here

Main incision The liver extended three inches below the costal margin in the midline There were about 32 ounces of yellow

low the base of the lung, and encapsulated The amount of pus present was about 400 c c On the posterior aspect of the lung and in the midline, in the region of the fifth and sixth dorsal vertebrae, there was

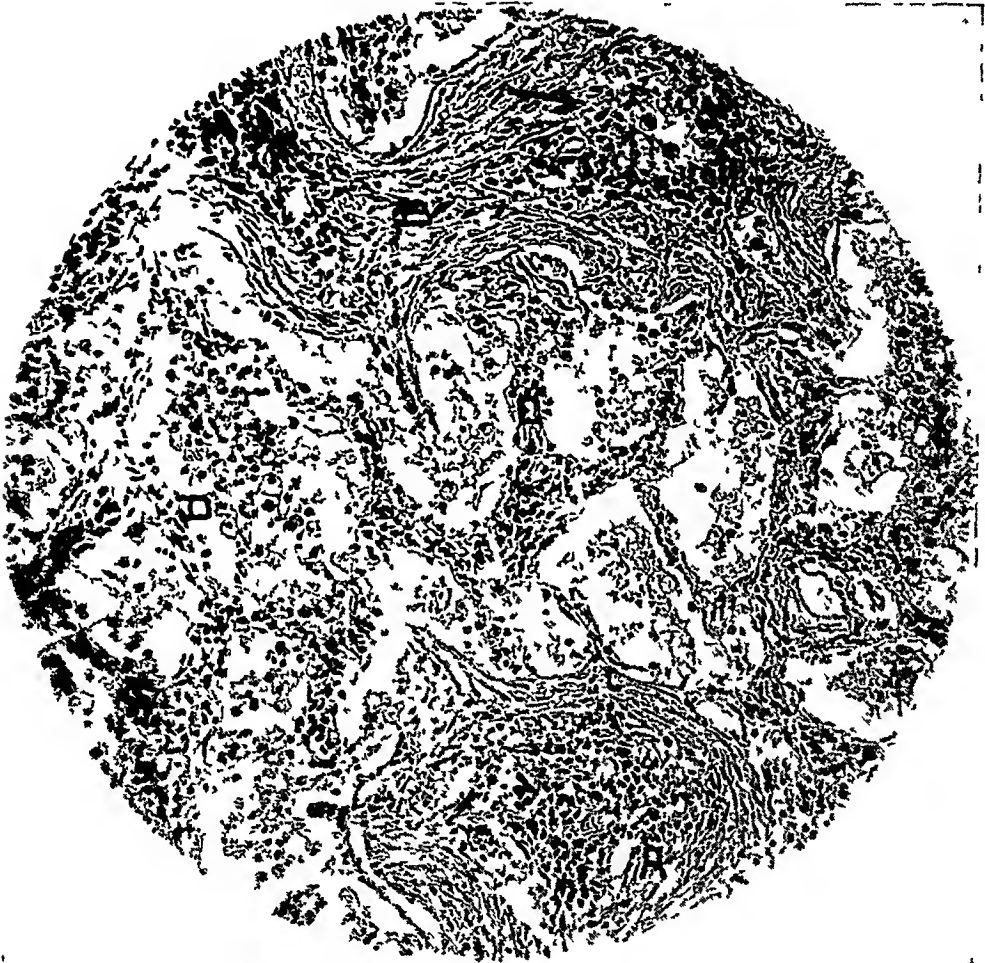


FIG 5 Organizing pneumonia in syphilis A Alveolus entirely obliterated by fibroblastic tissue which is rather rich in cells of the small round and histiocytic type B Hyperplasia of interstitial tissue of the lung C A band of fibroblastic tissue bisecting an alveolus D An alveolus containing numerous large round cells, (exfoliated alveolar epithelia) The arrow points to an almost obliterated alveolus

fluid in the peritoneal cavity The pericardial sac contained 25 c c of clear fluid The left pleural cavity contained one quart of straw colored fluid

The *left lung* was adherent to the chest wall, and from the base a copious thick purulent exudate escaped, coming from an area situated above the diaphragm and be-

noted a bulging of the descending branch of the aorta Just below the bifurcation of the bronchi on the left side and postero-lateral, there was found a well circumscribed area the size of a golf ball, which contained about 10 c c of thick purulent material In apposition to the upper portion of the lower left lung was found a sacculated aneurysm

The *right lung* was heavy and of a dark gray color, the pleura was thickened and the lung substance had a "shotty" feel

Lungs, trachea, esophagus, and aorta were removed in toto

The trachea was dissected down to the

The *aorta* had the described sacculated aneurysm, together with longitudinal striations of mother of pearl color and raised plaques with marked thinning of the wall.

The *lungs* on section showed diffuse tubercles and in the upper lobes of both lungs

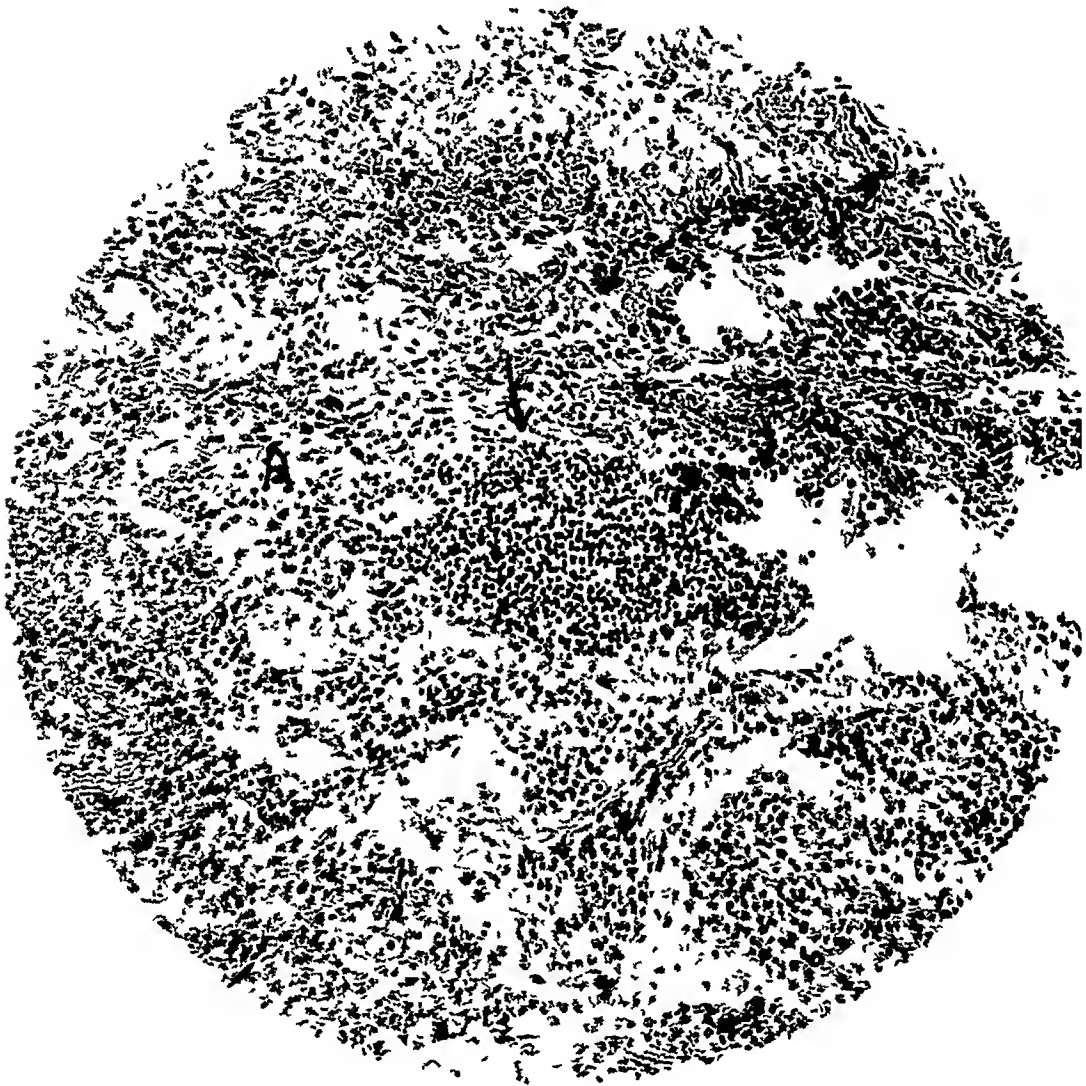


FIG 6 Syphilis of the lung The illustration shows productive inflammation induced by lues, practically no alveoli being preserved At 'A' is an area of replacement fibrosis The arrow points to a miliary gumma

bronchi and the left bronchus was dissected to its terminus A seeping hemorrhagic tract was noted extending from a small pinpoint perforation of the aneurysm into the substance of the posterior portion of the lower left lung The sacculated aneurysm, about the size of a lemon, was situated in the region of the fifth and sixth dorsal vertebrae

small cavitations and caseous material were observed In the lower lobes of both lungs there was carnification In the lower left lung there was an increased amount of stroma without aeration or crepitation Near the base of the left lung, about one inch below the hilus, there was a grayish, rubber like mass the size of a five cent piece The lungs presented the gray stage of hepatiza-

tion, and were firm throughout the whole middle and lower right lobes, and the upper left lobe

The heart showed a myocardium of good quality, its valves and orifices grossly normal

Microscopical Examination The heart showed focal areas of interstitial myocarditis, and chronic epicarditis. The *lungs* showed a chronic fibroid productive pneumonia. In some areas this was still in the active stage showing marked organization. In other areas it was characterized by definite fibrillated replacement of the lung parenchyma, areas of bronchopneumonia and areas of abscess formation. Examination likewise disclosed the presence of numerous focal collections of small round cells, invariably along the pulmonary interstitial stroma. These collections were considered pulmonary gummata. There was no evidence of tuberculosis or neoplasm. In one section there was a rather large hemorrhage, occurring not only in the parenchyma of the lung proper, but in a rather large number of the bronchioles. It was highly probable the result of the ruptured aneurysm. The *spleen* showed a chronic splenitis, congestion and edema. The *kidneys* showed congestion, edema and an early vascular nephritis, the *aorta*, a syphilitic aortitis.

Anatomic Findings Syphilitic aortitis, aneurysm of the descending thoracic aorta, chronic fibrinous pleurisy, empyema, encapsulated, left side, pneumonia, lobar type, gray stage, sero-fibrinous pleurisy of the right side with atelectasis of the lower right lung, atelectasis of the lower left lung, chronic passive congestion of the liver and spleen, acute nephrosis with vascular nephritis, hydropericardium, gumma of the left lung.

Syphilis of the lungs is rare and is seldom diagnosed clinically. In a search through the museums of the London Hospitals and the Royal College of Surgeons, Fowler⁴ found but twelve specimens. Two of these cases were doubtful. At the Johns Hopkins Hospital, Osler⁵ reported twelve cases out of 2,800 autopsies. Of these twelve,

only four were acquired. Among 3,000 autopsies at the Massachusetts General Hospital, Lord⁶ found only one case of acquired syphilis. Symmers,⁷ in a study of 4,800 autopsy protocols, 314 of which showed lesions of syphilis, reported twelve cases and syphilitic pleural lesions in two more (Orsten⁸). Of 110,258 admissions to Kings County Hospital between and including the years 1919 to 1925, a period of seven years, the number of syphilitic patients, diagnosed as such by a positive Wassermann reaction, the history, or physical signs, was 5,695. Not one of these was diagnosed as syphilis of the lung. Dr. Henry Monroe Moses,⁹ in a review of syphilis on his medical service at Kings County Hospital, between Dec 1, 1923, and March 1, 1926, found in a series of 2,450 patients, 191 diagnosed as having syphilis. These patients were usually in the late stages of the disease, and sought hospital treatment because of some intercurrent ailment, or because of disability due to syphilitic involvement of some organ or organs of the body. Of the 191 patients in this series, the intercurrent illness was in the lungs in fifty. There were twenty-four with pneumonia, eighteen with lobar and six with bronchopneumonia. There were twenty-six with pulmonary tuberculosis. All of these patients were acutely ill on admission. There were seven deaths among these fifty patients, with forty-three who recovered or felt well enough to demand their own release. Of the seven deaths one was diagnosed as pulmonary syphilis, but unfortunately an autopsy was not obtained.

Syphilis of the lungs occurs as the congenital form—so called white pneu-

monia—which is a diffuse fibroblastic proliferation with an interstitial infiltration of small round cells, and is seen in stillborn babies or those dying shortly after birth. It may occur also in the acquired form as a chronic interstitial pneumonitis or syphilitic phthisis. It may occur as gummata, which is the usual type, and be rather sharply defined with radiating strands into the lung tissue. In the case reported here, we have a combination of these two forms. Rossle² differentiates four types of the disease. He distinguishes (1) the cavernous syphilitic phthisis; (2) the gummatous, coarse, knotty form, (3) the coarse lobulated syphilitic scarred lung (*pulmo lobatus*), and (4), the coarse syphilitic callosity without pronounced changes of the exterior form or shape.

According to Councilman,¹⁰ the essential process in the production of a gumma in the lung is a pneumonia with fibrinous change in the alveolar walls, the whole subsequently undergoing caseation. The first step in the process is stated to be a hyaline degeneration of capillaries of the affected area. This is followed by atrophy of the alveolar walls. The alveoli become distended with large, pale, epithelial cells and fibrin, the cells also undergo hyaline degeneration, forming smooth bodies staining with eosin, and varying in size from one-half the diameter of a red blood corpuscle up to that of a large epithelial cell. The capillaries become converted into rigid tubes, and their lumina are much narrowed. Similar changes occur in the small veins and arteries. Immediately around the bronchi and arteries there is a forma-

tion of connective tissue, and here the alveolar walls show much thickening and contain many small round cells.

Gummata of the lung in elastic consistency resemble gummata found in other organs, occurring as nodules embedded in the tissues and surrounded on all sides by radiating fibrous strands. They may be single or in numbers, and may vary in size from that of a minute point as small as the smallest tubercle to the size of a hen's egg or larger, but the latter size is of rare occurrence. The central portion is firm, rubber-like, grayish white or yellowish like hard cheese. The necrotic, caseous part is analogous to that found in tubercles, but differing in its elastic, firm consistency and in its slighter tendency to liquefy. A section through a gumma in the lung tissue might have exactly the appearance of one from a large caseous encapsulated tubercle in the same situation. Buhl¹¹ was the first to call attention to the persistence of smooth muscle fibers in the pulmonary callosity in chronic pneumonitis, while Tanaka¹² and Rossle² found not infrequently smooth muscle in the lung in syphilitic processes. Demonstration of the spirochete or of the tubercle bacillus would not settle the matter, for Schmorl¹³ found spirochetes indistinguishable from *Spirochaeta pallida* in pulmonary gangrene and aspiration pneumonia, but these searches are notoriously discouraging of result.

The Wassermann reaction might afford important evidence. But as a rule the gross appearance and distribution of the lesions are found to be typical enough in each disease to allow one to

discriminate Gummata have a strong tendency to heal, so that they are commonly found as disappearing centers of caseous material in great radiating scars, at times causing strictures, deformities, or obstruction, as in a bronchus. The presence of these lesions on roentgen ray examination, in the absence of obvious tuberculosis and when other signs of syphilis exist, warrants a diagnosis of gummata, but doubtless many of those described may have been localized encapsulated tubercles, or having in mind the apparent rarity of lung syphilis, gummata may have been diagnosed as tubercles.

"Gummatous infiltrations have a tendency to occur around the hilus of the lung and in the lower lobe. Occasionally areas of lobular hepatization are observed" (Hala¹⁴). The walls of the bronchi or the large vessels at the hilum of the lung may be greatly thickened by the process, the adventitia of the vessels suffering. By pressure of gummata or stricture of scars, obstruction of a bronchus may occur with atelectasis of the lung field, or the so-called indurative bronchiectatic type of pulmonary syphilis may supervene.

"Whether pneumonic or ulcerative forms of syphilis with cavity formation really exist is uncertain" (MacCallum¹⁵). Fowler⁴ reports from the museum of Guy's Hospital a case of multiple gummata of the lungs, one of which was softening, breaking up and in the process of forming a cavity.

The confusion with tuberculosis makes this point difficult to settle (Flockemann¹), especially since syphilitics are prone to tuberculosis (twenty-six of 191 on our service at Kings

County Hospital during the years 1923 to 1925).

"In the diagnosis of pulmonary syphilis by the roentgen ray there is no characteristic picture"¹⁶ This diagnosis should be made only by the history, a positive Wassermann reaction and the result of antisyphilitic treatment (Jaches¹⁷). "In the light of our present knowledge, even a tentative diagnosis of pulmonary syphilis is not warranted until every other possible type of pulmonary disease is excluded" (Allison³).

"The history of the case, the Wassermann reaction, the bacterial findings, the distribution of the lesions and the relation to lesions elsewhere, the size, consistence and gross appearance, the tendency to heal or break down, the continued absence of tubercle bacilli in the sputum, and least of all, the histologic structure, are the things upon which a diagnosis of syphilis in the tertiary stage may be based" (Allison³).

From the complicated pathological descriptions of pulmonary syphilis it is not difficult to realize that the clinical picture of this condition is not characteristic. The symptoms simulate those of pulmonary tuberculosis, and the diagnosis of tuberculosis is usually made. MacCallum's description of the tertiary stage of syphilis and how difficult it is to differentiate it from tuberculosis, especially in the lungs, may be a good explanation for syphilis of the lung being so rare as an autopsy finding (Orsten).

There is presented here a patient having syphilis of the lungs proven by autopsy findings.

REFERENCES

- ¹FLOCKEMANN Neuere Arbeiten über Lungen-syphilis, zusammenfassendes Referat, Centralbl f allg Path u path Anat, 1899, x, 449-483
- ²ROSSLE, R. Über die Lungensyphilis der Erwachsenen, Munchen. med Wchnschr, 1918, LXV, 992-994
- ³ALLISON, R G Pulmonary syphilis, Am Jr Roentgenol, 1929, XXII, 21-24
- ⁴FOWLER, J K, and GODLEE, R J The diseases of the lungs, 1898, Longmans, Green and Co, London, 429, 435, 436, 438
- ⁵OSLER, SIR WM The principles and practise of medicine, 1918, D Appleton and Co, New York, 272
- ⁶LORD, F. T Diseases of the bronchi, lungs and pleura, 1925, Lea and Febiger, Philadelphia
- ⁷SYMMERS, D Anatomic lesions in later acquired syphilis, a study of 314 cases based on the analysis of 4,880 necropsies at Bellevue Hospital, Jr Am Med Assoc, 1916, LXVI, 1457-1463
- ⁸ORSTEN, G G Pulmonary syphilis, New York State Jr Med, 1926, XXVI, 541-545
- ⁹MOSES, H M Syphilis on a medical service, Am Jr Syph, 1926, x, 388-403
- ¹⁰COUNCILMAN, W T Syphilis of the lung, John Hopkins Hosp Bull, 1891, II, 34-37
- ¹¹BUHL Quoted by Schmitzler, H Zur Kenntnis der Lungen- und Trachealsyphilis, Wien klin Wchnschr, 1923, XXXVI, 829-832
- ¹²TANAKA, T Über die Veränderungen der Herzmuskulatur, vor allem des Atrioventrikularbündels bei Diphtherie, zugleich ein Beitrag zur Frage der Selbständigkeit des Bündels, Virchows Arch f path Anat, 1912, CCVII, 115-137
- ¹³SCHMORL, G Die pathologisch-histologischen Untersuchungsmethoden, 6 Aufl, 1912, F C W Vogel, Leipzig, 419
- ¹⁴POWER, H D'A, and HALA, W W Principles of pathology for practitioners and students, 1929, D Appleton and Co, New York, 426
- ¹⁵MACCALLUM, W G Text book of pathology, 1917, W B Saunders Co, Philadelphia, 650-653, 663
- ¹⁶ENTFIELD, C D X-ray evidence in diagnosis of gastric and pulmonary syphilis, Am Jr Syph, 1926, x, 621-624
- ¹⁷JACHES, L Roentgen-ray diagnosis, Virginia Med. Monthly, 1929, LV, 738-740

Observations on the Contour of Normal and Tuberculous Female Chests*†

By S A WEISMAN, M D, F A C P, *Minneapolis, Minn*

IN previous reports^{1, 2} various diameters of normal and tuberculous male chests were compared. They showed that the tuberculous chest was more rounded, longer, and deeper than the normal chest, and that the vital capacity was about forty per cent greater in the healthy chest. In this paper the normal and tuberculous female chests will be compared. For normals, three hundred University of Minnesota girls were examined in the Spring of 1930 at the Women's Gymnasium. For tuberculous chests the data obtained on one hundred and thirty-three tuberculous women at Glen Lake Sanatorium, Oak Terrace, Minnesota was used.²

The ages of the normal girls ranged from sixteen to twenty-four years and of the tuberculous group from sixteen to sixty years. In order to make the comparison as close as possible, the tuberculous cases were divided into two groups, fifty cases representing the ages sixteen to twenty-four and eighty-three cases representing the ages twenty-five to sixty.

THORACIC INDEX

The average thoracic index, which is the ratio of the depth of the chest

to the width, for three hundred University girls was 70.2. In comparing this average with those found by other investigators it was found that the Minnesota girls stand very high in chest development. Wilder and Pfeiffer³ in reporting measurements on one hundred students at Smith College, stated that because the girls came from all parts of the Union it represented an average for the womanhood of the United States. The average thoracic index reported by them was 72.3. This represents a more rounded and less developed type of chest than that found for the University of Minnesota women by about three per cent. The same technique and statistical methods were used as described in my previous reports.

Again in 1929, also from Smith College, Steggerda, Crane and Steele⁴ reported measurements on one hundred girls. The average thoracic index found by them was 75.2, which is 6.5 per cent deeper than that of our series. Their findings show a much deeper and more rounded form of chest.

The thoracic indexes for our series of tuberculous chests were

Group I, ages 16 to 25, 73.3,

Group II, ages 25 to 60, 72.1

After determining the probable error for the two groups and for the normals and computing the difference in terms of probable error, the findings

*From the Department of Medicine, University of Minnesota, and the Glen Lake Sanatorium, Oak Terrace, Minn.

†Received for publication, June 2, 1931.

are of some significance in comparing the two groups

In comparing the normals with the first group of tuberculous chests, both ranging from sixteen to twenty-four, the difference in terms of probable error is 4.2. This indicates definitely that the tuberculous chest is more rounded than the normal

ceptible to tuberculosis. Malone⁵ and Hall⁶ have shown by means of pantographic tracings that the better developed chest is flat and has a greater vital capacity. Muller⁷ and Hutchinson⁸ have shown that the chest of the fetus is deeper than it is wide. Scammon and Rucker⁹ have demonstrated that a baby's chest at birth is nearly round,

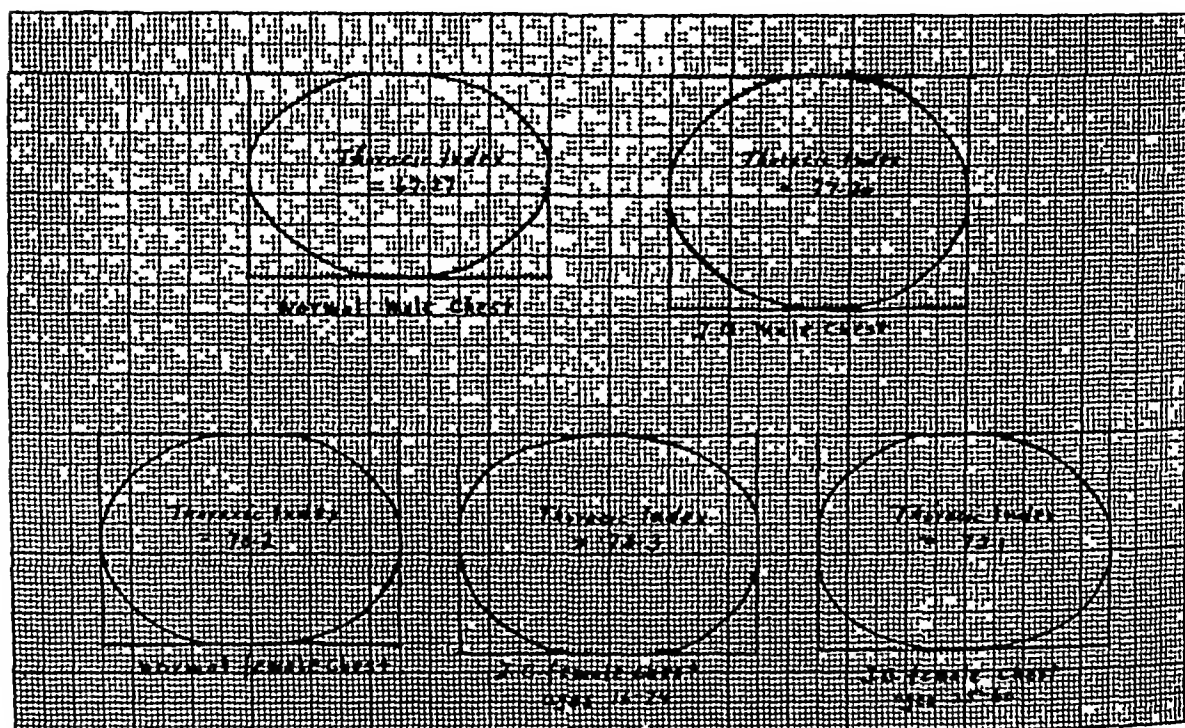


FIG 1 Diagrammatic sketches of chest diameters

In comparing group II, ranging in ages from twenty-five to sixty, with the normals, the difference in terms of probable error is probably, but not certainly, significant, namely 2.67

The above figures tend to show that the older tuberculous group have a flatter and better developed chest than the younger group. This fact emphasizes a point brought out in previous reports,^{1,2} that the deeper, rounded chest is an undeveloped one, it is the primitive chest, it has a lower vital capacity, and it is, perhaps, more sus-

ceptible to tuberculosis. Zeltner¹⁰ has shown that the chest becomes more flattened up to the twentieth year, and Stewart¹¹ states that the vital capacity at about the twentieth year is the greatest. At this age the chest begins to change toward the infantile type and slowly assumes a more rounded form until development ceases at about the sixtieth year, as shown by Weisenberg.¹²

Therefore one should expect an older person to have a more rounded chest than a younger one, and an older individual with tuberculosis should surely have a more nearly round or deeper chest than a younger one afflicted with the same disease. Our findings, however, show the opposite to be true

osis, it had a better vital capacity and warded off the disease until later in life

Draper¹³ in his book, "Human Constitution," gives the measurements of twenty-eight tuberculous female chests. The thoracic index was calculated as 74.5 which is a more rounded chest

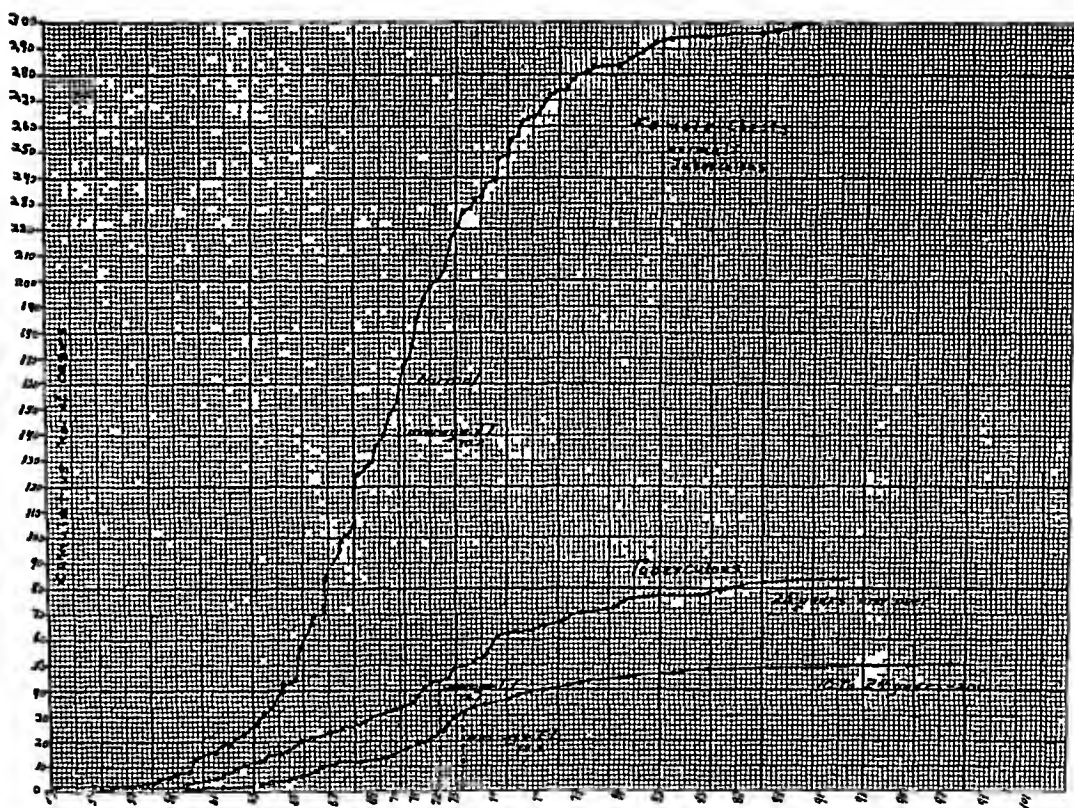


FIG 2 Cumulative number graphs of thoracic indexes in groups of women considered

The older tuberculous group have flatter and better developed chests than the younger tuberculous group. This perhaps indicates that the nearer round or the less developed the chest is in early life, the more liable is that individual to develop pulmonary tuberculosis. The flatter chest, like that found in group II, probably means that that chest was more resistant to tubercu-

than either of our groups. The difference, as with other investigators mentioned above, may have been due to the technique used. In our series the normal female chest was found to be more rounded than the male. Rodes¹⁴ showed that the female negro chest is narrower than the male. Draper, too, showed that the female white chest is narrower than that of the male. Jack-

son¹⁵ has shown that the average chest expansion and vital capacity in the female is less than it is in the male In our series² of six hundred and five University of Minnesota male students the thoracic index was found to be 67.27.

THE SUBCOSTAL ANGLE

The subcostal angle in the normals and two tuberculous groups was measured. A definite difference between the normal and the diseased chests was found The average for the three hundred normal girls was 75.9° and for group I of the tuberculous, 68.7°. The difference in terms of probable error is 5.46. The average for group II of the tuberculous is 71.1° The difference in terms of probable error is 4.8 These findings, too, are in accord with those of the thoracic index, that the older tuberculous group has a better developed chest than the younger group

AGE

The average age for the three hundred normal girls was 18.7 years, and for the tuberculous group I, 21.1 years The range in both of these series was

between ages sixteen and twenty-four Tuberculous group II ranged from twenty-five to sixty years. The average age was 31.7 years

COMMENT

As was emphasized in the previous reports, perhaps it is wise to again stress the importance of measuring, as a routine, the chests of children In this way one is more able to find those with undeveloped chests, chests that are perhaps more susceptible to tuberculosis Proper exercises can help improve the undeveloped chest Gotz¹⁶ working with children, and Turner's¹⁷ recent report of results on young female adults show that proper exercises increase the vital capacity of the lungs

CONCLUSIONS

- 1 Female tuberculous chests are shown to be more nearly round and deeper than the normal.
- 2. There is a possibility that the rounder the chests the earlier in life is one apt to contract tuberculosis
- 3 There is evidence that proper exercises in early life can stimulate chest development.

TABLE I

Summary of Indexes of Thoracic Measurements (Female)

Type	Thoracic Index	Subcostal Angle	Average Deviation		Probable Error	Difference in Terms of Probable Error				Age	
			Thoracic Index	Subcostal Angle		Thoracic Index	Subcostal Angle	Thoracic Index	Subcostal Angle	Range	Average
Normals	70.2	75.9°	4.46	4.48	±0.229	±0.256				16 to 24	18.7
Tuberculous*											
Group I	73.3	68.7°	3.00	10.2	±0.695	±1.33	4.2	5.46		16 to 24	21.1
Group II	72.1	71.1°	6.00	9.81	±0.675	±0.978	2.67	4.80		25 to 60	31.7

*The thoracic index of the tuberculous female chests reported in my previous paper (2) is 72.6 instead of 72.1 (Error in printing)

REFERENCES

- ¹WEISMAN, S A Contour of normal and tuberculous chests, Jr Am Med Assoc, 1927, LXXXIX, 281
- ²WEISMAN, S A Further observations on the contour of normal and of tuberculous chests, Arch Int Med, 1929, XLIV, 29-36
- ³WILDER, H H, and PFEIFER, M W The bodily proportions of women in the United States, based upon measurements taken from one hundred Smith College students, Am Acad Arts and Sci Proc, 1924, LIX, 441-603
- ⁴STEGGERDA, M, CRANE, J, and STEELE, M D One hundred measurements and observations on one hundred Smith College students, Am Jr Phys Anthropol, 1929, XIII, 189
- ⁵MALONE, F R The relation of chest contour to lung capacity, Jr Am Med Assoc, 1904, XLIII, 783
- ⁶HALL, W S Mathematical relations of certain chest measurements, Jr Am Med Assoc, 1904, XLIII, 787
- ⁷MÜLLER, CHARLOTTE Zur Entwicklung des menschlichen Brustkerbes, Morphol Jahrb, 1906, XXXV, 591
- ⁸HUTCHINSON, WOODS Some deformities of the chest in the light of its ancestry and growth, Jr Am Med Assoc, 1897, XXIX, 512
- ⁹SCAMMON, R E, and RUCKER, W H Changes in the forms and dimensions of the chest at birth and the neonatal period, Am Jr Dis Child, 1921, XXI, 552
- ¹⁰ZELTNER, E Thorax Studien, Munch med Wchnschr, 1919, LXVI, 1407
- ¹¹STEWART, C A The vital capacity of the lungs of children in health and disease, Am Jr Dis Child, 1922, XXIV, 451
- ¹²WEISENBERG Quoted by Zeltner (reference 10)
- ¹³DRAPER, GEORGE Human constitution, 1924, W B Saunders Company, Philadelphia
- ¹⁴RODES, C B The thoracic index in the negro, Ztschr f Morphol u Anthropol, 1906, IX, 102
- ¹⁵JACKSON, C M Physical measurements of the female students at the University of Minnesota, with special reference to body build and vital capacity, Am Jr Phys Anthropol, 1929, XII, 3
- ¹⁶GOTZ, H Modification of child chest by gymnastics, Monatschr f Kinderh, 1925, XXX, 97
- ¹⁷TURNER, A H Vital capacity in college women, Arch Int Med, 1930, XLVI, 938

American Mountain Tick-Fever—Semiography and Nosology

With Remarks on Pathology and Treatment*

By NOXON TOOMEY, M D , F A C P , *Palmyra, Mo*

THE tick borne fever of the mountainous areas of western North America has on several occasions since 1850 been the subject of brief remarks and of other publications of a more comprehensive character. It cannot be said, however, that the disease has ever been adequately described. All of the early and more recent descriptions of the disease show the want of knowledge concerning its etiology, its epidemiology, and its immunological relationships. Indeed, the published observations on the American mountain tick-fever have been for the most part either fragmentary or confused by the observers' preconceived ideas.³ Nevertheless, it would be unjust to carp at the memoirs on mountain fever that were written by W. T. Ewing,⁴ by Roberts Bartholow,⁵ by John J. Milhau,⁶ by Charles Smart,¹⁴ and by Charles F. Kieffer,⁴⁰ as those observers deserve great credit for recording accurate and succinct descriptions of the disease as observed by the unaided eye.

What has been most remarkable is not the essential inadequacy of early descriptions of the mountain or non-exanthematic tick-fever, but the fact

that it has been necessary for the present writer to re-discover it, at least from the aspects of calling attention to its existence and of establishing it as a separate disease entity.^{47, 18}

The non-exanthematic tick-fever of the mountains has a characteristic clinical course, but a course that varies with its virulency to range from a mild, remittent-recurring type of fever to a severe typhoidal form. In the latter type the fever is so continued as to virtually obscure the remittent and recurrent characteristics. Some cases commence with marked remittency of the fever but pass into a continued fever, high or low, with more or less stuporousness and prostration. These two types, the recurrent and the continued (with more or less remissions) have been noted by most observers. They were treated as separate types by Kieffer,⁴⁰ and will provisionally receive like treatment by us, but with the qualifying remark that the continued form is very probably tularemia, but has not yet been proven to be so. These types are not absolutely fixed but are observed to somewhat intergrade with one another, which lends color to the belief that mountain fever may occasionally take a continued fever

*Received for publication, Aug 29, 1931

form In some localities the recurrent type of the fever is more characteristic than in other localities, thus in the Black Hills and in Wyoming the fever is predominantly recurrent whereas in Colorado and Utah it is more commonly observed to have one well marked major episode followed by one, or at the most two, very minor exacerbations A distinct tendency to a remittent and recurrent character can, however, be almost always made out even in the so-called continued type, and similarly in the Colorado-Utah type with one major episode, the recurrences are often so minor in character as to frequently attract no special attention

CLINICAL COURSE

With but very few exceptions, the *incubation period* is four days Longer incubation periods have been observed but seven days is the longest authentic instance Kieffer observed a case with an incubation period of three days

The *prodromes* consist of extreme weariness and faintness (languor), loss of appetite, muscular weakness, and an "empty or sinking feeling" in the epigastrium They merge with and continue throughout the onset, which usually occurs within two to eight hours after the first appearance of malaise

The *onset* is sudden with profound chilliness (but with no rigor) lasting from one to two hours and alternating with occasional flashes of heat The cold stage is suddenly succeeded by a rapid accession of fever, accompanied by excruciating pains in the back and loins, and to a somewhat less extent throughout the body, especially the posterior cervical region and the extremities, with occasional cramping

of the legs A diffuse dull headache, chiefly frontal, occurs commonly but is rarely severe, although occasionally intolerable The muscles become tense and the small muscles twitch, particularly the orbiculars and those of the face Nausea is usually noticed Vomiting is usually absent in adults but may occur in children, although not as commonly as in other fevers The face becomes flushed, the facies tense and troubled, the skin hot and dry, the tongue red and swollen ("strawberry tongue"), the conjunctivae very markedly congested, but lachrymation does not occur

The pulse, at first rapid (85 to 90), full and bounding, becomes, after a few hours, very rapid (120 to 130), thin and tense and continues so for twenty-four to forty-eight hours

The *fastigium* is characterized by a fever of 103.4° to 104.6° F, by the patient lying motionless, for fear of pain on motion, but with a clear though restless sensorium, sleep being impossible, or broken and troubled Breathing is shallow, a trifle quickened and sighing Meteorism does not occur

Constipation is the all but invariable rule throughout the course of the disease, the patient usually going four or five days without defecating Should evacuation take place spontaneously there is great tenesmus and pain in the anus, the feces being scybalus and covered with mucus, frequently blood tinged

The tongue, at first congested ("strawberry tongue"), becomes swollen, large and flabby, with a

very thick, moist bluish-white glaze of pasty (cheesy) consistency to the very tip, latterly cracking down the center. The tongue is tremulous when protruded.

Urination is impeded by muscular tenesmus, or almost entirely suppressed, or if any urine is passed it is scanty and highly colored, causing scalding when voided.

The liver and spleen, and all the muscles are tender to touch, the deep bone and joint and muscle pains continuing, but without redness or swelling of the joints.

Perspiration begins gradually and continues scanty for twenty-four to thirty-six hours, to end in a moderate (but seldom drenching) sweat coincident with the rapid lysis that ends the febrile period at the end of the second or early part of the third day. With defervescence, the congestion of the conjunctivae and face, the headache, and muscle aches, subside, the patient being left free from pain, but prostrated.

No erythema or other cutaneous manifestation develops at any time, but after the final defervescence a fine branny desquamation of the skin may occur.⁴ The latter is not common and seems due to medication with antimony or arsenic.

On the fourth day after the first accession of the fever, the patient feels very well, and desires to be up and about, but on the fifth to sixth day in a large proportion of the cases the fever, weariness, and muscle pains return, but with much less severity than at first, and last only from twelve to eighteen hours. After this recurrence subsides the

patient convalesces slowly, except that there may be one or two more recurrences of the fever to a slight degree.

On and after the fifth day the countenance assumes a dull despondent expression, the face a dirty yellowish hue, with a tinge of dark brown in the cheeks.

Usually the total duration of the disease is eight or nine days, although not uncommonly ten days. Very exceptionally it may be as much as fourteen to twenty-six days, especially so when of the continued fever type. Some slight cases run their course in five or six days, but some of the latter cases, if observed under the advantages of hospital care would be recognized as of the eight day duration.

Convalescence is characterized by marked anemia, by a persistence in the sensation of weariness throughout the whole body, and weakness and stiffness of the joints of the extremities. The carpo-metacarpal, metacarpal-phalangeal, and phalangeal joints are sometimes especially stiff and painful.¹⁴ Bartholow believed that "In many instances, the first evidence of commencing convalescence, was a violent pain in the soles of the feet, increased at night."¹⁵

VARIATIONS IN THE CLINICAL COURSE

The prodromes very exceptionally drag on for two or three days (in cases with a seven day incubation period), but more commonly than being prolonged they are less than three hours in duration, the disease striking suddenly. Very frequently slight muscle pains are noticed during the prodromal stage, but they do not become excruciating.

ating until the onset The onset is never free from pain, but in mild cases the muscle and bone pains develop gradually after the initial chilliness has passed off The initial epigastric distress is sometimes described as a hunger pain

The chilliness is sometimes so slight as to escape the observation of the patient Sometimes the initial chilliness is distinctly intermittent, alternating every fifteen minutes to one hour with like periods of sweating and a sense of heat, the intermissions occurring approximately hourly for the first twenty-four hours, or until the fastigium is well established

Nausea is very variable, in some outbreaks being a prominent symptom and occurring frequently before or with the onset of the chilly (initial) stage If it has not occurred during the invasion it is extremely unlikely to occur during the fastigium Vomiting occurs fairly frequently in children, but not as commonly as in other fevers In adults, vomiting almost never occurs, or at least not without great difficulty (about ten per cent of the cases) due apparently to a cardiospasm On the other hand, there are exceptional cases in adults in which vomiting occurs repeatedly with each onset of a febrile paroxysm

The headache is occasionally described by patients as being intolerable, and feeling very much as if the head were being mashed between rollers

The perspiration is occasionally established early and gives a cold clammy feel to the skin after the initial chilliness has existed for an hour or so Equally frequently the skin is hot and dry, and moist and cool by turns, alter-

nating at eight to twelve hour intervals The perspiration of the rapid lysis is always marked, and occasionally deserves the characterization of a drenching sweat, but usually it does not On the whole, very noticeable hyperidrosis is not a characteristic of mountain fever

A low, more frequently violent, delirium may occur during the fastigium, and recurrently at the height of each febrile paroxysm It is most likely to be observed in alcoholics, nephritics and others with an impaired metabolism

Occasionally, but very exceptionally, the bowels become spontaneously relaxed after the second or third day (once only as a rule) The stools, dark brown and watery and containing scybalous masses, are extremely offensive in odor Meteorism has been observed in exceptional instances

In mild cases the patients do not go to bed but drag around complaining of feeling "out of sorts", stupid and sleepy, with loss of appetite, constipation, and aches and pains in the bones and joints, or "neuralgias"

The fever typically lasts for forty-eight hours and recurs with less intensity after an intermission of forty-eight hours, the paroxysms of fever and intermissions being each of two days duration, but the fever becomes progressively less severe with each remission A general type of regularity can be made out, and some of the early epidemics described by army surgeons evidently ran with few exceptions to the regular type encountered during the epidemic described, but on the whole mountain fever is not as regularly remittent and recurrent as malaria is intermittent Irregularity of the

remittences and recurrences is common so that mountain fever is best described as a fever distinctly irregular but with marked tendencies to a regular type

The various observed febrile courses can be reduced to a graphical portrayal as follows

Numbers in parentheses represent days of fever, other numbers, days of intermission. Accents represent degree of intensity: two, severe; one, moderately severe; none, mild. Figures (2) (1) and (1) (1) mean that a nearly complete or very decided remittance occurs between the days indicated but lasts for only a relatively brief time

v=vomiting, d=delirium, =convalescence, x=one, two or three additional (usually mild to moderately severe* recurrences)

(2)" 2 (2)' 2 (1)	16 per cent
(2)" 2 (1) 3 (1)	5 per cent
(2)" 2 (2)' 2 (2) x	6 per cent
(2)' 2 (2)" 2 (2) x	3 per cent
(2)' 2 (2)" 2 (1)	5 per cent
(2)' 2 (2)" 2 (1) 1 (1)	3 per cent
(2)" 2 (1)'(1) 2 (1) 1 (1)	10 per cent
(2)" 2 (1)'(1)' 2 x	5 per cent
(1)"(1)' 2 (1)(1) 2 (1)	5 per cent
(1)"(1)" 2 (1)'(1) 2 (1)	5 per cent
(1)"(1)" 2 (1)'(1) 2 x	2 per cent
(3)" 2 (2)' 1 (1)	10 per cent
(2)"(1)' 2 (2) 1 (1)	6 per cent

*These percentages merely represent our impression as to the approximate frequency with which the different combinations of remittance and recurrence occur. It is not to be supposed that the above groups exhaust all combinations that may be encountered, but they well exemplify the "irregular regularity" of mountain fever.

The 'days' as given, particularly as referring to the days of intermission, are not to be understood to be exact periods of twenty-four hours. In fact there is not as exact a diurnal cycle seen in mountain fever as in the paludisms.

(2)"(1)' 2 (2) 1 \	2 per cent
(2)"(1)' 2 (1)(1) 1 x	2 per cent
\(2)" 2 (2)' 2 (1)	2 per cent
v(3)" 2 (2)' 1 (1)	1 per cent
v(2)"(1)' 2 (2) \	2 per cent
\(2)" 2 v(1)' 2 (1)	1 per cent
(2)"d 2 (2)'d 2 \	3 per cent
(2)"d(1)'d 2 (2)'d 2 \	1 per cent
(2)"d(1)'d 2 (1)d(1) 2 (1)	2 per cent
v(2)"d 2 (2)'d 2 \	1 per cent
v(2)"d(1)'d 2 (2)'d 2 x	1 per cent
v(2)"d(1)'d 2 (1)d(1) 2 (1)	1 per cent

PHYSICAL FINDINGS

The marked conjunctival engorgement has already been noticed. Epistaxis may occur but is decidedly uncommon. The fauces are normal or slightly injected but never extremely hyperemic. There is no buccal endanthem. Cervical and other external adenopathy is not noticeable.

Chest findings are not a part of the disease but a secondary bronchitis sometimes follows the disease when inclemencies of the weather have been experienced during the pyrexial period.

Abdominal discomfort, always present to some extent, is vague, variable, and inconclusive. Rigidity and hyperesthesia, and pain on deep palpation, are to be discounted as the patient is hyperesthetic and tense over the whole body. The spleen becomes barely palpable early in the course of the disease but does not become more than slightly enlarged. The liver is always tender and sometimes a trifle enlarged. A distended bladder may be encountered.

DIAGNOSIS

Mountain fever is particularly devoid of characteristic (pathognomonic)

physical findings Not one of the physical findings may not be found in some other fever or even group of fevers The nearest approach to an exception is the tongue, which is fairly characteristic, and yet by no means pathognomonic Hence diagnosis must rest, in the present state of our knowledge, upon a consideration of the attending circumstances (locality, season, history of tick bite or of exposure), exclusion of other possibilities, and upon the appearance of the clinical phenomena as a whole, the latter being unique when considered with respect to their syndrome and evolution The differentiation from the two most clinically similar diseases, dengue fever and relapsing fever, will be discussed under the heading of nosography

Owing to the history of tick-bite, the disease that gives rise to the greatest practical difficulty is spotted fever of the Rocky Mountains Where mountain fever and spotted fever co-exist locally it is not to be supposed that mountain fever can always be distinguished from spotted fever during the first two days of its course After the second or third day, however, spotted fever should be excluded by a consideration of the following clinical differences

Spotted fever has a somewhat less stormy onset with a more protracted accession of fever, with a continued and prolonged (and usually ultimately higher) character, with only slight or moderate remissions Important, also, are the lesser intensity of spotted fever's muscle and bone pains, the stupor developing in spotted fever after the second or third day (even in mild cases, although not in the mildest, ambulatory, type) The lesser degree of nausea but the more marked cyanosis and hyperidrosis in spotted fever are

usually noticeable after about thirty-six to forty-two hours The puffy facies of spotted fever contrasts with the pinched facies of mountain fever The spotted fever case lies relaxed, "log-like", the mountain fever case is more tense, for fear of pain on movement In spotted fever insomnia is all but absolute, in mountain fever it is only relative, sleep occurring fitfully A dry cough, with or without a small amount of very tenacious mucus, occurs with the prodromal stage or onset of spotted fever but is not present at all, or only very late, in the course of mountain fever By the fifth or sixth day the spleen is larger in spotted fever than in mountain fever The tongue tends to remain more swollen and much less coated in spotted fever than in mountain fever, and frequently cannot be protruded in spotted fever Finally one of the most helpful and invariable differences is the absence of the characteristic lenticulo-macular (initially slightly raised) erythematocyanotic (frequently hemorrhagic) exanthem of spotted fever, which first appears on the ankles and wrists and extends upwards to cover the trunk but (usually) spares the face A perhaps inconstant difference, and yet one helpful at times, in the early course of the disease, is that the abdominal symptoms of spotted fever at onset suggest an acute cholecystitis (or hepatitis) whereas those of mountain fever suggest a cardiospasm with ulcer or gastric dilatation symptoms

As the continued form of mountain fever may be very difficult or impossible to distinguish from mild or aberrant types of typhoid fever and the paratyphoids, no attempt will be made to describe the (inconstant) clinical differences except to call attention to the semi-liquid stools, the occipital instead of frontal headache, the small, dry tongue, the ultimate bradycardia, the greater wasting of body tissues, the scaphoid abdomen, and the odor of body and breath encountered in the enteroides group It is of course understood that agglutination tests or

blood cultures may be necessary for definitive diagnosis for both the enteroid group and tularemia, which will also frequently have to be taken into consideration

Acute epidemic influenza has undoubtedly been mistaken for mountain fever, and accounts for some of the so-called mountain fever reported in the winter months¹⁰ The much greater irregularity of its remittances, the profuse lachrymation, rhinorrhea and sneezing, the acutely congested pharynx, with frequent secondary otitis and nasal sinusitis, the symptoms of bronchial involvement, the larger, more compressible pulse, the more superficial character of the muscle aches, with particular predilection for the intercostal and cervical groups, the (occasional) singultus, and the tendency to a critical or epicritical diarrhea, make up a clinical picture that ought not to be mistaken for mountain fever.

Regional septic processes, perinephric abscess for example, may cause a heavily coated tongue and an irregularly-regular type of remittent fever, but with them the generalized intolerable "break-bone" pains are absent, whereas a sharp, knifstab-like, or deep "hot iron," regional pain is present

PATHOLOGY

No necropsy material has been available

The *urine* shows nothing noteworthy During the prodromal stage the patient often passes much clear urine of low specific gravity The urine drawn during or after the fastigium is of high specific gravity, acid, and with excess of pigments and bladder epithelium, but is free of sugar, ace-

tone, bile and albumin unless some renal impairment has already been present Hyaline casts may be found

The *blood* shows a profound change, especially so considering the intensity and short duration of the fever The red cells become greatly reduced; in severe cases to 3,000,000 or even to 2,500,000, which is less than fifty per cent of the normal red count at high altitudes Hemoglobin diminishes in ratio with the red count, the color index remaining 1, although when regeneration commences the red cells increase at greater rate than the hemoglobin, the index falling below 1. The anemia is predominantly a toxic, aplastic, rather than a hemolytic anemia, although the muddy color of the face late in the disease suggests the occurrence of some hemolysis.

Neither a leucocytosis nor a leucopenia develops although the white count tends to range a trifle above normal The differential count shows a constant increase of the large mononuclears (150 to 165 per cent) with lymphocytes around ten per cent and eosinophiles under 1 per cent The large mononuclears are increased absolutely as well as relatively, a condition also noted in spotted fever

The absence of jaundice speaks for very little derangement of the liver or bile ducts

Numerous cases of mountain fever studied repeatedly in the laboratory at the Post Hospital of Fort D A Russell have shown conclusively that the serum of mountain fever does not contain the typhoid organism nor agglutinate the latter

So far, numerous efforts to establish the disease in guinea-pigs have failed

This is one of the best evidences that the virus is distinct from that of spotted fever

PROGNOSIS

In mild cases convalescence is more rapid than in dengue but in severe cases it may be prolonged for weeks. Organic complications or local sequelar infections do not develop, except very rarely the cutaneous pyodermata in those who are uncleanly and already debilitated, with chronic foci of staphylococcic or streptococcic infection.

Mortality is not indisputable, but is extremely rare at best. In the early literature several deaths attributed to the continued form of the disease were recorded but the true nature of these cases is uncertain, much of the severe, so-called mountain fever undoubtedly having been typhoid fever^{16, 17, 20, 26, 33} or tularemia. And yet there is no reason why a severe case of mountain fever should not carry off a debilitated individual or a patient embarrassed by cardiac insufficiency.

TREATMENT

The patient should be put to bed and made comfortable, blankets and hot water bottles, or tepid sponging, being used according to the stage of the disease. A large hot toddy or hot lemonade is grateful. Emetics were formerly much employed but are of doubtful value unless retching is continued and troublesome.

During the initial episode, and severe recurrences, morphine should be given hypodermatically in effective dosage every four hours, as it alone relieves the excruciating bone and muscle pains. For the milder recurrences, acetphenetidm or the less efficacious acetylsalicy-

lic acid will be satisfactory, acetanilid should be avoided. To quiet the sensorium a hypnotic such as barbital, fifteen or twenty grains, should be given and repeated as necessary, or a bromide in sixty grain doses is usually sufficient, chloral hydrate should be avoided. A collyrium of half saturated boric acid solution to which a fifth-part of epinephrin chloride solution (1-1000) has been added is grateful to the eyes. If photophobia is noticeable a dark cloth should be placed over the eyes unless the room can be completely darkened. An alkaline, antiseptic mouth wash should be prescribed for frequent use. An isotonic solution made of equal parts of salt and baking soda does equally as well. The bowels should be moved, preferably by enema in the early stage of the disease, but, as soon as the onset has passed off, by a saline cathartic or by a hydragogue cathartic pill, such as the calomel-rhubarb-colocynth pill, repeated daily for two or three days. The bladder should be watched, and if necessary to prevent distension, the urine should be drawn. Digitalis is rarely indicated, as in spotted fever, except in the continued fever type of the disease, when it is well to start it early.

Other than to place the patient on a sensible fever diet, with thought being given to the constipation, no special dietary restriction is necessary. During convalescence, the severe anemia should be combated by means of an iron, arsenic and copper hematinic, and cod liver oil according to indications. For ending the persistent joint aches, a short course of sodium or potassium iodide in large dosage, with or without

a little Fowler's solution, is distinctly valuable

There is no known specific for the disease. Quinine was formerly much employed, and much abused, but impartial observers as Milhau⁶ and Kieffer,⁴⁰ early discovered that it not only had no effect on the fever but in large doses did harm by increasing the subjective symptoms.

Kieffer attached considerable value to subcutaneous injections twice daily of one or two cubic centimeters of a one per cent solution of sodium arsenite to which four per cent cocaine hydrochloride was added to control the pain. We feel that neither the sodium arsenite nor sodium cacodylate injections are necessary, but that Fowler's solution by mouth in appropriate but fair-sized dosage will do as much good. It should not constitute routine treatment but should be reserved for cases that continue to run a fever after the seventh day, or have protracted muscle aches and joint pains.

NOSOLOGY

The non-exanthematic tick-fever of the mountainous West evinces a syndrome not unlike, in some respects, the clinical course of two diseases, each of which is the type of a different disease category, namely dengue fever and relapsing fever. As to which category it is more nearly correct to assign the American mountain fever can be determined for clinical purposes, but for a final assignment on the basis of bacteriological and pathological evidence it will be necessary to await the study of the virus of mountain fever. Other fevers have a recurrent clinical course, such as undulant fever (brucel-

lasis, melitococcemia) but it would for the present seem to labor a point to go beyond a consideration of mountain fever's two most presumable cognate affinities.

Compared with the relapsing fever group we find that mountain fever and the relapsing fevers are arthropod-borne diseases, that neither are invariably exanthematous; that both are characterized by a marked secondary anemia, and that both have well marked recurring or relapsing characteristics. There are these differences however: the relapsing fevers are caused by *Spirochaeta* that are not difficult to recover from the blood at some time during the clinical course; they are notable for being truly relapsing virtually to their final episode, which is seldom the second or third relapse. They prostrate, but do not cause the profound bone, joint and muscle pains that are practically a fixed character of mountain fever. The relapsing fevers have a comparatively insidious onset and a much greater interval between relapses than does mountain fever. They frequently cause a bronchitis and a disorder of the cornea not observed in mountain fever. Finally they are of the bilious type with icterus occurring in one-fourth to one-half of the cases, according to the severity of the epidemic.

Compared with dengue fever we find that mountain fever is of like short duration, that it is, like dengue, more properly called recurrent than relapsing, and that the disease is of equally, or nearly equally, abrupt onset. It has in common the "break bone" symptoms, the congestion of the conjunctivae, and the absence, or virtual ab-

sence, of bronchial involvement Mountain fever differs from dengue fever in lack of a palmar and plantar erythema and a generalized erythematous or polymorphous eruption. Also there is not the cervical adenopathy that one finds in thirty per cent to seventy per cent of the cases of dengue. Lachrymation occurs in dengue but not in mountain fever. The tongue is not greatly different in the two diseases although more heavily coated in mountain fever. Constipation is not so absolute in dengue, purging being observed in about one-third of the cases. Mountain fever differs in producing a far greater anemia and in not being accompanied by the characteristic and well marked leucopenia of dengue. In both fevers there is an increase of the large mononuclears, but the eosinophiles are increased only in dengue.

From the above comparisons it will be observed that mountain fever has an intermediate position between the short fevers of the dengue type and the protracted fevers of the relapsing fever group. Similar in some reactions to the one and yet in other reactions more closely resembling the other, it serves almost as a 'connecting link', were one to take cognizance of the theory that dengue is a spirochetal disease. We do not wish it understood that we are asserting a theory of mountain fever's spirochetal nature, but when one considers the comparative difficulty with which the *Leptospira icterohemorrhagica* is recovered from the blood in the spirochetal type of infectious jaundice, a protozoan of some such character may occur in the blood of mountain fever, and yet have escaped detection. In this connection it should not be for-

gotten, however, that Noguchi recovered from the mountain fever tick, *Dermacentor andersoni*, a filterable virus that was demonstrated not to be the virus of spotted fever.⁴⁴ Whether the filterable virus recovered by Noguchi is that of mountain fever remains to be ascertained.

Apparently mountain fever has closer affinities to dengue fever than to relapsing fever but whether the resemblance is sufficient to warrant grouping it provisionally with dengue fever may well be a matter of opinion, but, keeping in mind that it is but tentative, it would seem permissible clinically to group mountain fever with dengue fever.

THE CONTINUED FORM OF MOUNTAIN FEVER—POSSIBLY TULAREMIA

Appearing from the outstart as a continued fever, or more commonly becoming a low continued fever after an initial phase with remittences, this type of mountain fever tends to a longer course than the remittent type. Two weeks to twenty-six days is the usual duration, but in Colorado and Utah, and occasionally in Wyoming, a shorter fever of nine or ten days may be predominantly of the continued type, although some minor degree of remittance can usually be made out.

The continued form is somewhat typhoidal as far as the fever and the nervous system are concerned, but with those exceptions there is not a close resemblance to typhoid fever. The continued form seems to be a lower grade of infection limited largely to the blood stream. In it the muscle-bone-joint pains and other localizing phenomena are not nearly so severe. Towards the

end of the disease the patient is weaker and more emaciated than after the short recurrent type, but convalescence is not thereby prolonged, it being by no means unusual for these cases to convalesce somewhat more rapidly than those who had a typical recurrent type of American mountain tick-fever but continued to have persistent bone and joint pains during convalescence

There is very considerable reason to suspect that the so-called continued type may not be due to the virus of American mountain tick-fever but to a *Bacterium tularensense* infection. The local lesions, acute but indolent skin ulcers at site of tick bites, typical of tularemia, occur following tick-bite in some of these cases, but they certainly have not been observed in all

REFERENCES

- ¹WAGGONER, F R On the mountain or continued miasmatic fever of Colorado Territory, *Am. Jr Med Sci*, 1850, N S, I, 50-55
- ²BOYLE, C E On mountain fever, *St Louis Med and Surg Jr*, 1851, IX, 454-456, and *Ohio Med and Surg Jr*, 1851, III, 528-530
- ³OATMAN, J E Mountain and malarious fevers produced by the same cause, *Boston Med and Surg Jr*, 1851, XLIV, 511-512, and *Northwest Med and Surg Jr*, 1851, VIII, 105-108
- ⁴EWING, W. T Mountain fever, *St Louis Med and Surg Jr*, 1855, XIII, 109-116
- ⁵BARTHLOW, ROBERTS Sanitary reports, Camp Scott, Dec 1857, and Utah Territory, Sept 1858 Statistical Report on the Sickness and Mortality in the Army of the U S, Jan, 1855, to Jan, 1860 Wash, D C, 1860 CCXCIII, 302-304
- ⁶MILHAU, JOHN J Sanitary report, Sixth infantry en route to Utah, Sept 1858 Stat Rep. on Sick and Mort in Army of U.S 1855 to 1860 Wash, D C, 1860 304-306
- ⁷BREWER, CHARLES Sanitary report, Fifth infantry, Utah, Dec 1859 Stat Rep on Sick and Mort in Army of U S 1855 to 1860 Wash D C, 1860 310-314
- ⁸LOGAN, THOMAS M Report on the medical topography and epidemic diseases of California, *Trans Am Med Assoc*, 1866, XVI, 497-569
- ⁹HOGG, A J Report from Medicine Bow, Wyoming Territory, Circular No 8, U S Army, Report on Hygiene of the U S Army, Wash, D C, 1875, p 361.
- ¹⁰VOLLUM, E P Sanitary report, Camp Douglas, Utah. Circular No 8, Report on Hygiene of U S Army, 1875, p 340
- ¹¹PATZKI, J H Sanitary report, Fort Steele, Wyoming Territory Circular No 8, Rep on Hyg of U S Army, 1875, p 385
- ¹²TOWNE, F L Sanitary report, Fort Shaw, Montana Circ No 8, Rep on Hyg of U S Army, 1875, p 434
- ¹³JACQUETTE, Assistant Surgeon Sanitary report, Fort Boise, Idaho Circ No 8, Rep on Hyg of U S Army, 1875, p 480
- ¹⁴SMART, CHARLES On mountain fever and malarious waters, *Am Jr Med Sci*, 1878, 17-43
- ¹⁵REBER, C T Mountain fever and malarious waters, swamp fever and marsh miasm, *St Louis Med and Surg Jr.*, 1880, XXXVIII, 448-451
- ¹⁶HOFF, JOHN VANR Typho-malarial fever, the so-called "mountain fever" of the Rocky Mountain region *Am Jr. Med Sci*, 1880, LXXIX, 38-59
- ¹⁷WOODWARD, J J Memorandum, *Am Jr Med Sci*, 1880, LXXIX, 59-60
- ¹⁸BESHOAR, M Mountain fever, *Rocky Mount Med Rev*, 1881, I, 328
- ¹⁹Mountain fever and pneumonia, *Calif Med Jr*, 1882, III, 397, 433
- ²⁰NEWTON, RICHARD COLES A case of mountain fever, *Phil Med Times*, 1882, XIII, 7-9
- ²¹THOMPSON, JESSE E "Mountain fever," *St Louis Courier of Med*, 1884, XII, 298-307
- ²²CURTIN, ROLAND G Rocky Mountain fever, *Trans Am Climat Assoc*, 1887, III, 190-197

- ²³DOUGAN, D H Rocky Mountain fever, Trans Am Climat Assoc, 1887, III, 191-193
- ²⁴HUBER, L The so-called mountain fever of Colorado and adjacent regions, its description and treatment, Med News, 1890, LVII, 278-281
- ²⁵TREACY, W Mountain fever, Times and Register, 1890, LVI, 75-78
- ²⁶CAMPBELL, W A The identity of typhoid and the severer forms of so-called mountain fever, Trans Colorado Med Assoc, 1892, 207-229, also Med News, 1892, LXX, 479-482
- ²⁷WORK, HUBERT Mountain fever, Med News, 1893, LXXII, 376-378
- ²⁸ADAMS, W E Mountain fever, Med Herald, St Joseph, 1895, N S, LVI, 480-482
- ²⁹WALKER, J M Mountain fever and its relation to typhoid, Trans Am Inst Homeop, 432-446, 1897
- ³⁰RAYMOND, E I A peculiar mountain fever, Med World, 1897, xv, 452
- ³¹RAYMOND, HENRY I Mountain fever, Am Jr Med Sci, 1898, CXV, 276-294
- ³²GEISENDORFER, J A Some peculiar forms of enteric fever, Med Sentinel, 1898, VI, 8-10
- ³³STUVER, E Mountain fever, Med News, 1899, LXXXV, 577-581
- ³⁴ORMSBY, E A Bilious typhoid or mountain fever, Calif Med Jr, 1899, XX, 225-228
- ³⁵WOODRING, W W Mountain fever, Denver Med Times, 1902, June
- ³⁶WILSON, L B, and CHOWNING, WM M The so-called "spotted fever" of the Rocky Mountains A preliminary report to the Montana State Board of Health, Jr Am Med Assoc, 1902, XXXIX, 131-136
- ³⁷WILSON, L B, and CHOWNING, WM M Report on the investigation of so-called spotted fever 1st Bien Rep Montana St Bd Health, 1903, 26-91
- ³⁸ANDERSON, JOHN F Spotted fever (tick fever) of the Rocky Mountains A new disease, Bull No 14, Hyg Lab, U S Pub Health and Mar Hosp Serv, 1903, 50 pp
- ³⁹WILSON, L B, and CHOWNING, WM M Studies in *Pyroplasmosis hominis* ("spotted fever" or "tick fever" of the Rocky Mountains), Jr Infect Dis, 1904, I, 31-57
- ⁴⁰KIEFFER, CHAS F Intermittent tick fever Preliminary report on a new type of fever due to tick bite (ixodiasis), Jr Am Med Assoc, 1907, XLVIII, 1154-1158
- ⁴¹STILES, CHAS W The common tick (*Dermacentor andersoni*) of the Bitter Root Valley, Pub Health Rep, U S Pub Health and Mar Hosp Serv, 1908, XXIII, 949
- ⁴²INTERNATIONAL COMMISSION ON ZOOLOGICAL NOMENCLATURE Opinion No 78, Smithsonian Miscel Coll, 1924, LXXIII, 1-14
- ⁴³BECKER, F E Investigations on Rocky Mountain spotted fever in Colorado, Jr Infect Dis, 1926, XXXIX, 81-88
- ⁴⁴NOGUCHI, H Filter-passing virus obtained from *Dermacentor andersoni*, Jr Exp Med, 1926, XLIV, 1-10
- ⁴⁵PARKER, R R Rocky Mountain spotted (tick) fever, Bull Nevada St Bd Health No 9, 1929, 3-17
- ⁴⁶BECKER, F E Tick borne disease in Colorado, Colorado Med, 1930, XXVII, 36-43, 87-95
- ⁴⁷TOOMEY, NOXON Mountain fever and spotted fever of the Rocky Mountains—Clinical studies, Ann Inter Med, 1931, v, 585-600
- ⁴⁸TOOMEY, NOXON American mountain tick-fever and spotted fever of the Rocky Mountains—comparative epidemiography, Ann Inter Med, 1931, v, 601-612

Bilateral Double Kidney With Duplication of Ureters*

BY ROBERT M. LINTZ, M.D., Brooklyn, N. Y.

ANOMALIES of the various parts of the body are not infrequent, but with the exception of those of the spine those occurring in the genito-urinary tract are most often noted¹. One of the rather frequent anomalies of the genito-urinary tract is that of double kidney with duplication of renal pelves and of the ureters. Young and Davis² state that the *condition* of double kidney and ureter is not so rare, but that the *recognition* of the condition is extremely rare. They believe that anomalies of the kidney and ureter are much more frequent than is generally appreciated and that among such kidneys a relatively large number show pathological changes, malformation predisposing to disease.

Various types of duplication of the ureter with the accompanying double kidney have been reported from time to time. It is possible to have unilateral involvement with the other side normal or both sides may be changed from the normal. In the condition known as complete duplication of the ureters there are separate bladder orifices for each ureter with the ureters running from the pelves to the bladder. This means that where there is

complete bilateral duplication there are four ureteral orifices present in the bladder. In the incomplete form of duplication there is union of the duplicated ureters somewhere between the emergence from the pelves and the entrance into the bladder. In these cases the bladder may present the usual appearance as far as the ureteral orifices are concerned. Where there is complete duplication of one side and either a normal opposite side or incomplete duplication of the opposite side three ureteral openings into the bladder will be present.

Thompson³ reported fifteen cases of duplication of renal pelves and ureters in 1735 consecutive autopsies at London Hospital and three cases in 11,133 consecutive autopsies performed at Guy's Hospital and at Victoria. It is interesting to note that of the eighteen cases of duplication sixteen were females. Mauclaire and Sejourne⁴ found the ratio of occurrence in females to males to be 7 to 3. Thompson's observation is at considerable variance from those of some of the earlier investigators. Wagner,⁵ Poirier,⁶ and Bostroem⁷ in large autopsy series found the frequency of complete and incomplete duplication of the ureters to be from three to four per cent. Braasch and Scholl⁸ cited 144 cases of

* Received for publication, May 8, 1931.

duplication of renal pelves and ureters of which thirty per cent were complete and seventy per cent incomplete. Of these 144 cases there were only eight (5.5 per cent) in which bilateral duplication of pelves and ureters was present and all of these eight did not have four bladder orifices for the ureters. These authors also noted that 37.5 per cent of the cases presented some pathology of the urinary tract. Harpster, Brown and Delcher⁹ in a review of the cases of duplication of the ureter in the literature up to 1922 found complete duplication in 58.1 per cent of the 382 cases reported up to that time. They recorded 181 instances of complete unilateral duplication, 40 of complete bilateral duplication, 133 of incomplete unilateral duplication, and 28 of incomplete bilateral duplication. They believe that only a very few cases of this condition are diagnosed pre-operatively, the difficulty being increased when the cystoscopic examination shows but two apparently normal ureteral openings in their usual positions.

From the number of cases of this form of anomaly of the urinary tract that are cited one might conclude that this condition should be encountered

infrequently in practice. That the diagnosis is seldom made is well known. The figures that have been quoted are derived from autopsy records or from observations made on a large series of operative cases. Mertz,¹⁰ in 1920, compiled a list of the cases of duplicated ureters recorded to date. He came to the conclusion that many cases are discovered only post mortem and that of those diagnosed during life and before operation the diagnosis

was possible only after repeated urological and x-ray examinations.

My purpose in here citing another case of bilateral double kidney and ureters is twofold: first, to point out that with the aid of newer laboratory methods this condition should be diagnosed more frequently; second, to show that the responsibility for this diagnosis need be borne no longer solely by the urologist but that the responsibility rests upon internist and the general practitioner as well, with the aid of the roentgenologist.

REPORT OF CASE

Case. A single woman, a school teacher, age 52, came October 18, 1930, complaining of pain and discomfort in the left lower quadrant of the abdomen and in the left lumbar region, the latter radiating at times down the left thigh. The pain had been present for as long as the patient could remember but had recently become more annoying. Lately there had been frequency of urination; she noted that on urination there was accentuation of the pain of the left side of the abdomen and of the left thigh. For the last four years there had been epigastric distress after eating, during this interval the patient was frequently awakened from her sleep by migrainous headaches. There was nothing of significance in the previous history. The family history was interesting in that her mother died at the age of 45 years with carcinoma of the bladder and one sister has been told that she has calculi of the urinary bladder.

The patient was well developed and very well nourished. Her height was 5 feet 1½ inches and her weight was 161 pounds. There was a systolic murmur over the apex of the heart which was considered as functional in nature. There was marked tenderness to palpation below the right costal border over the area of the gall bladder. No lumbar tenderness was noted. Other features of the physical examination were essentially normal. The blood pressure was 122/90. A tentative diagnosis of gall bladder disease and nephrolithiasis was made.

The patient had 4,220,000 erythrocytes and 6,700 leukocytes. The differential count showed 60 per cent polymorphonuclears, 2 per cent eosinophiles, 2 per cent large lymphocytes, and 36 per cent small lymphocytes. The hemoglobin was 90 per cent (Sahli). Repeated examinations of catheterized urine showed a few white blood cells and numerous red blood cells.

Cholecystography (after the oral administration of tetra-iodo-phenolphthalein-sodium) showed a gall bladder that filled satisfactorily and was reported as normal in size and shape and regular in contour. In the fundus of the gall bladder there was a small circular filling defect about the periphery of which there was a thin dense shadow. This concentric rim was visible two hours after the gall bladder had been emptied of the dye by the ingestion of a fat-full, mixed meal. A report of cholelithiasis was made.

It was considered unlikely that the biliary calculus was accountable for the left sided pain. Due to the persistent presence of blood cells in the urine the diagnosis of renal calculus was further advanced. The kidneys were x-rayed and there was no evidence of calculi. Both kidneys were reported as being considerably larger than usual. The patient was then given 40 grains of Uroselectan (sodium salt of 2-oxo-5-iodopyridine-N-acetic acid) intravenously. Twenty minutes after the intravenous injection of the dye there was a very clear visualization of two renal pelves on each side from each of which a ureter came off (figure 1). On both sides the more superior pelvis consisted of but a single calyx while the inferior and larger pelvis had two major calyces. A moderate degree of hydronephrosis of the two lower pelves was reported more pronounced on the left side. On each side the ureter from the superior pelvis was situated medial to the one from the inferior pelvis. A picture made forty-five minutes after the dye had been injected gave no additional information. In the picture made sixty minutes after the dye had been given (figure 2) the ureters in their lower course are well seen. On the left side two distinct shadows placed very close together are noted down to the level of the symphysis pubis. Below this a single wider shadow is noted

entering the bladder. It could not be ascertained definitely from the picture whether this represented a union of the duplicated ureters or whether it was due to overshadowing of the separate ureters. Although the right side did not show this condition so clearly, a similar arrangement could be made out on very close inspection of the films. The patient was referred for cystoscopic examination, but inasmuch as she refused this examination it could not be definitely made out whether two, three, or four bladder orifices were present.

Papin and Eisendrath¹¹ pointed out that the ureter belonging to the upper pelvis always ends lower and more medially. In addition, they state that when there are two ureters from one kidney there are always two pelves on that side—no case has ever been shown to be otherwise. Bugbee and Losee¹² held that the presence of a double ureter means the existence not only of two pelves but also of two physiologically separate kidneys on the side involved, although these may be fused anatomically to represent a single organ. Braasch and Scholl⁸ were of the opinion that hydronephrosis is the most common pathological complication of duplication of the ureters. They believed that this is most probably due to the fact that there is ureteral obstruction in the region of the junction of the two ureters in incomplete duplication. Harris¹³ was of the same opinion and added that there is usually nothing in the history or physical examination to lead one to suspect anomalies. Thompson found that the combined capacity of the pelves in double kidney may be less than that of a single normal pelvis. In such cases the gradual constriction of the normal pelvis may be replaced by a very sharp one, making the discharge of urine



FIG 1 Twenty minutes after the intravenous injection of the dye. The arrow indicates the biliary calculus, this might easily be mistaken for a renal calculus if cholecystography had not been successful



FIG 2 Sixty minutes after injection of the dye On the left side the course of the lower part of the ureters is clearly seen

more difficult. He believes that at times pain and slight pyuria can be explained only on the basis of double small pelvises with reduplication of ureters.

EMBRYOLOGY

The following brief summary of the embryological development of the urinary tract is taken mainly from the article of Young and Davis.² During the embryological development of the higher vertebrates there are three successive types of excretory organs. These are the pronephros, the mesonephros, and the metanephros—the latter becoming the permanent kidney. All three types come from the mesodermal blocks known as the nephrotomes. The nephrotomes consist of a series of blocks of mesodermal cells situated longitudinally along both sides of the neural canal and are between the primitive segments and the lateral mesodermal plates.

The Wolffian duct—the excretory duct of the mesonephros—is formed from the pronephros. The mesonephros arises from the nephrotomes that extend from the fifth cervical to the third lumbar segments and consists of a series of glomeruli and tubules opening into the common duct. In man this structure atrophies. According to Kelly and Burnam¹⁴ the mesonephros is at the height of its development during the fourth and fifth weeks of embryonic life. The mesonephros atrophies during the eighth to sixteenth embryonic weeks, the Wolffian duct persisting as the vas deferens in the male and as the rudimentary Gartner's duct in the female.

The Wolffian duct opens into the cloaca and it is near this juncture that

a budding occurs which is the anlage of the permanent kidney. From this bud is formed the ureter, pelvis, calyces, and collecting tubules while the secreting portion of the kidney is formed from a collection of mesodermal cells known as the metanephrogenic tissue. This latter mass of tissue surrounds the tip of the ureter bud soon after its formation.

The ureteral bud, capped with metanephrogenic tissue, first grows dorsally toward the spine and then turns cranialward. The tip of the bud at the 6 mm embryo stage has become bulbous and as early as 8 mm a bifurcation of the primitive pelvis occurs, the first evidence of the calyces. During the ascent of the kidney the uro-rectal septum appears, dividing the cloaca into what is to be rectum and bladder. Young and Davis believe that in double ureter the cause may be ascribed to premature or exaggerated bifurcation of the ureteral bud, the split extending varying distances down the ureteral stalk instead of being confined to the primitive pelvis.

COMMENT

The frequency of the occurrence of double kidney with duplication of the ureter and the very infrequent diagnosis made of this condition suggests that there is generally a nearly complete absence of symptoms that might be termed characteristic. When a patient does give a story that might be referable to the urinary tract, such an anomaly is rarely considered. With the aid of cystoscopic examination the frequency of diagnosis of double ureter is somewhat increased, but still the possibility of missed diagnosis is too great.

Assuming that retrograde pyelography is employed it is usual to visualize but one ureter where there is incomplete duplication. A reflux of the contrast medium into the lower portion of the accompanying ureter is usually the first hint of duplication of the ureter.

Where a history and physical examination are suggestive of an indefinite disturbance of the urinary tract the physician should consider the possibility of double ureter. With the introduction of intravenous pyelography the diagnosis becomes quite easy and very certain. This method, as is well known, is easy of application. The certainty with which the diagnosis is made or ruled out in kidneys of good function is apparent. Employment of this method makes for a more comfortable and satisfied patient. Where intravenous pyelography is used it may make cystoscopic examination unnecessary—a procedure to which many patients object both before and after its accomplishment.

It is to be expected that the preoperative diagnosis of double kidney and double ureter will be more frequent. The presence of this condi-

tion can usually be determined very satisfactorily by the internist or the general practitioner with the aid of an x-ray study.

CONCLUSIONS

1. The occurrence of double kidney with duplication of ureters and kidney pelves is not rare, but the diagnosis is seldom made.

2. Pain in the lower quadrant of the abdomen and in the lumbar region of the same side radiating down the thigh, frequency of urination, red blood cells and white blood cells in the urine, should lead one to consider the possibility of this anomaly after renal calculi have been ruled out.

3. Duplication of ureters and pelves is due to an abnormal exaggeration of the usual embryonal development.

4. Intravenous pyelography enables easier and more certain diagnosis of double ureters and pelves than does cystoscopy.

5. With proper x-ray studies the internist and the general practitioner should make the diagnosis of this condition.

REFERENCES

- ¹POTTER, R. P., and SEXTON, W. G. Anomalies of ureters and kidney pelves, *Radiology*, 1929, XII, 199-206.
- ²YOUNG, H. H., and DAVIS, E. G. Double ureter and kidney, with calculous pyonephrosis of one-half, cure by resection, the embryology and surgery of double ureter and kidney, *Jr Urol*, 1917, I, 17-32.
- ³THOMPSON, A. R. Congenital deformities of upper urinary tract, being a continuation of previous papers on horseshoe kidney and solitary kidney, *Guy's Hosp Rep*, 1929, LXXIX, 351-364.
- ⁴MAUCLAIRE, M., and SEJOURNET, P. Duplicité incomplete de l'uretere droit, *Bull et mém Soc anat de Paris*, 1910, LXXXV, 963-965.
- ⁵WAGNER, P. Angeborene Missbildungen der Nieren, Nierenbecken, und Harnleiter, *Handbuch d Urol*, 1904, II, (Frisch und Zuckerkand) Alfred Holder, Vienna.
- ⁶POIRIER, P. Sur quelques phénomènes consécutifs aux injections urétérales, *Compt rend Soc de biol*, 1891, 95, III, 585-587.
- ⁷BOSTROEM, E. Beiträge zur pathologi-

- schen Anatomie der Nieren, 1884, 1, Berlin und Tubingen, J C B Mohr, Freiburg
- ⁸BRAASCH, W F, and SCHOLL, A J JR Pathological complications with duplication of renal pelvis and ureter (double kidney), *Jr Urol*, 1922, VIII, 507-546
- ⁹HARPSTER, C M, BROWN, T H, and DELCHER, H A Abnormalities of kidney and ureter, a case of double kidney and double ureter with a review of literature, *Jr Urol*, 1922, VIII, 459-490
- ¹⁰MERTZ, H O Bilateral duplication of the ureters with a compilation of recorded cases, *Urol and Cutan Rev*, 1920, XXIV, 636-640
- ¹¹PAPIN, E, and EISENDRATH, D N Classification of renal and ureteral anomalies, *Ann Surg*, 1927, LXXV, 735-756
- ¹²BUGBEE, H C, and LOSEE, J R The clinical significance of congenital anomalies of the kidney and ureter, with notes on the embryology and fetal development of the kidney, *Surg, Gynec and Obst*, 1919, XXVIII, 97-116
- ¹³HARRIS, A Interesting anomaly of complete duplication of ureters and renal pelvis with review of literature, *Urol and Cutan Rev*, 1929, XXXIII, 300-302
- ¹⁴KELLY, H A, and BURNAM, C F Disease of the kidneys, ureters and bladder, with special reference to the disease in women, 1914, D Appleton and Co, New York

On the Treatment of Angina Pectoris

“THE spiritual side of the case must not be neglected in this disease in which the emotions play so important a rôle. The development of a philosophy of life, of the power of adaptation of desire to possibilities, the cultivation of hobbies of a restful character, such as suitable reading, music and such pacific occupations as painting, etching, carving and similar pursuits, are of real medical benefit. Habits of restfulness and relaxation are to be cultivated. Climate is often very important, and those who live in the temperate zones may well spend their winters in the South or perhaps go to live permanently in some mild, temperate and congenial climate. Few patients do well in the cold places or at high altitudes.”—(HARLOW BROOKS, M D, F A C P, *Am Jr Med Sci*, 1931, CLXXXII, 784-800)

Editorial

INTERNAL RADIATION IN THE CAUSATION OF MALIGNANCY

A few months ago reference was made editorially in the *ANNALS* to the known extrinsic factors having a carcinogenic or sarcogenic action. X-ray and other solar irradiation have both been recognized for many years as belonging in this group. That the radio-active source may be within the body of the victim, inseparable from him, diminishing in amount and activity only by its natural and unalterable decay, and at the same time be capable of inducing neoplastic proliferation in a startling conception. Martland¹ has demonstrated that this is exactly the situation which obtains with certain of the radium dial painters. Knowledge of this fact has a significance much wider than its application to this extraordinary occupational disease. It may explain the extrinsic factor in certain other forms of occupational malignancy and sounds a warning in connection with the indiscriminate internal use of sources of radio-activity.

The circumstances under which radium poisoning was recognized as an occupational disease are now well known. In a New Jersey factory there were employed for varying periods of time during the years 1917

to 1924, about 800 girls whose work was painting the luminescent dials of watches and clocks. The paint consisted of phosphorescent zinc sulphide combined with small amounts of radium, mesothorium and radiothorium in the form of insoluble sulphates. Due to the habit of pointing the brushes used between the lips, small amounts of radio-active paint were ingested over extended periods. The possibility of absorption through the skin and by inhalation also existed. Subsequent investigations have shown that, while most of the paint ingested passed rapidly through the alimentary tract and was eliminated, a certain portion was stored in the body and particularly in the bones. After final deposition in the bones these radio-active substances emit their characteristic radiations continuously, diminishing only with the exhaustion of the deposit by the natural process of physical-chemical decay, a process so slow in the case of radium that a life-time makes no significant change. It has been found from material obtained at autopsy that the lethal amount of radio-active substances distributed in the entire skeleton may range from 10 to 180 micrograms, estimated as radium element. As Martland vividly states it, it is necessary to have only 10 micrograms (one one-hundred-thousandth gram) of radium bromide, distributed over the entire skeleton, to

¹MARTLAND, HARRISON S. The occurrence of malignancy in radio-active persons, *Am Jr of Cancer*, 1931, xv, 2435-2516

produce a horrible death years after it has been ingested. The damage in the radium dial painters is due to the internal bombardment with alpha particles, a type of radiation never before known to have occurred in human beings.

Martland has knowledge of 18 deaths, among the former employees of this factory, which can be strongly suspected of being due to so-called radium poisoning. Eight were proved to be such by autopsy. In addition, there are about 30 persons alive who are suffering from typical symptoms of radium poisoning or who, by virtue of their internal radio-activity, are liable to develop crippling lesions at any time. During the first six years after the development of this industry the ill-effects and resulting fatalities fell into two chief groups. One of these was characterized by a radiation osteitis, with a superadded bacterial infection in the case of the mandible and maxilla, so that extensive necrosis of the jaw preceded the fatal outcome. In the other group the continuous bombardment of the bone marrow resulted in a regenerative type of leukopenic anemia which resisted all efforts at treatment. During the years of this earlier period, that is, from 1922 to 1928, two dial painters died from osteogenic sarcomas. These were reported in 1929 by Martland and Humphries² who recognized that the incidence of two cases of sarcoma among fifteen examples of radium-mesothorium poisoning was too large

to be passed over as due to coincidence. This belief has now been fully justified for Martland's more recent report records the results of autopsy studies upon three more fatal cases of anaplastic osteogenic sarcoma, all of the victims coming from the group who worked in the New Jersey factory. In addition, he lists three additional living cases of probable osteogenic sarcoma from the New Jersey group and another fatal case in a girl who had worked as a dial painter in factories in other states.

In view of the known incidence of primary bone sarcoma in the general population, the occurrence of so many examples in the limited group exposed to this occupational hazard can have but one explanation—internal radiation has operated as a causal factor. Actual malignancy has been preceded by radiation osteitis, associated at first with a hyperplastic, irritative, compensatory bone marrow which is succeeded by a replacement fibrosis. The aplastic marrow of external irradiation is not found.

Knowledge of an occupational hazard should lead to its mitigation and eventual elimination. The demonstration of this sarcogenic agent has a wider significance, however, than its importance in the dial-painting industry. It affords a basis for a high degree of certainty that the occupational primary carcinoma of the lungs, which has been the most common cause of death among the cobalt miners of the Schneeberg district in Saxony for five hundred years, is best explained by the radio-activity of the ore. The air of these mines has a radio-active ema-

²MARTLAND, HARRISON S., and HUMPHRIES, ROBERT E. Osteogenic sarcoma in dial painters using luminous paint, *Arch Path.*, 1929, vii, 406-417.

nation content of from a few to 50 Maché units. A high incidence of primary carcinoma of the lung is said to have appeared among the workers in the pitchblende mines of Joachimsthal. It must be accepted that the deposit of radio-active substances in the body, particularly those producing alpha rays, may give rise to malignancy many years afterwards. From

this, it follows that the indiscriminate lay and quack use of radio-active waters, emanators, activators, etc., should be stopped. They are without therapeutic value aside from their psychic effect and may be doing an, as yet, unrecognized harm. It may be learned that even slight increase in the normal radio-activity of the human body is not without danger.

San Francisco—The City by the Golden Gate

SINCE the American College of Physicians will hold its Sixteenth Annual Clinical Session in San Francisco, April 4 to 8, 1932, it is appropriate to call attention at this time to certain facts of general and historical interest about the city in which we are to gather

San Francisco is not only one of the world's most beautiful and fascinating cities, it is also the center from which nine-tenths of California's scenic wonders can be most easily reached. Within a few hours' easy journey by train, stage or car are most of the places which tourists come thousands of miles to see. Yosemite lies due east, and can be easily reached in seven hours by automobile or train. Monterey Peninsula—one of the finest strips of sea coast in the world—is three and one-half hours by train to the south. The giant redwoods begin right in San Francisco's suburbs, at Muir Woods,

and can be visited in half a day's excursion.

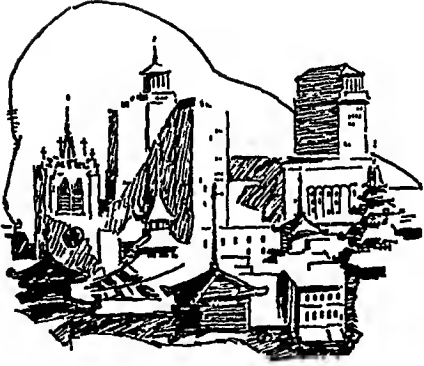
Lake Tahoe, at the summit of the Sierra, is an easy night's or day's run by train or a short detour *en route* or returning. Shasta, Lassen, Sequoia National Parks, the Redwood Empire, the wine-grape valleys, Stanford and California Universities, Luther Burbank's gardens, Jack London's Valley of the Moon—all are within the circle of San Francisco excursions, requiring from a few hours to a day or two.

ONE OF THE WORLD'S TRULY COSMOPOLITAN CITIES

San Francisco is famous for its gay spirit, its Chinatown, its beaches, its picturesque waterfront, its flavor of Asia and the sea, its French and Italian restaurants, its Parisian touch. Not so many realize that it is also the business capital of the West and a seaport.



San Francisco's skyline from the Bay



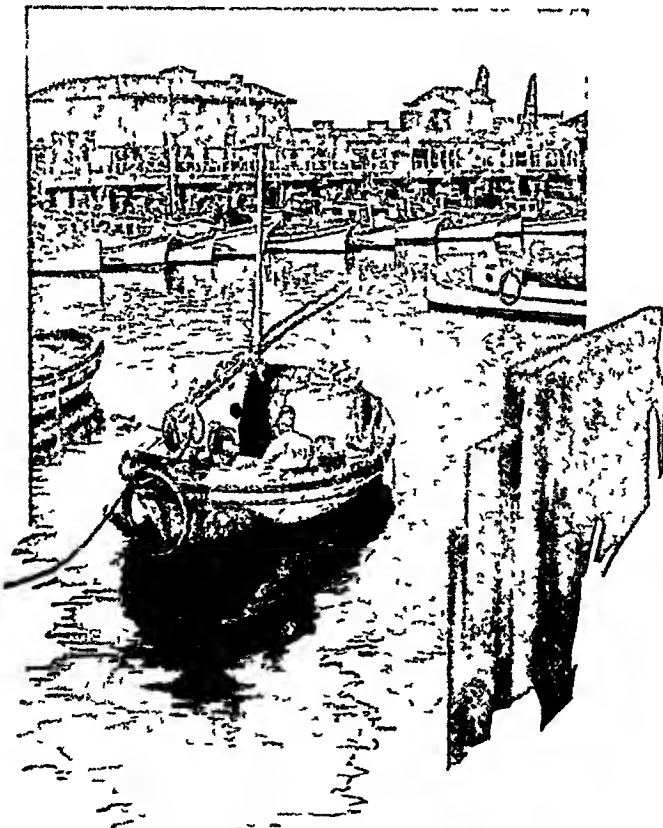
Cosmopolitan scene

insurance, commercial and industrial enterprises that function from Chile to Alaska and from Salt Lake City to Shanghai and Singapore

A TOWN TO PLAY IN

From the days of the Gold Rush, San Francisco has believed in laughter and good living. People on the streets are happy and cordial. They smile easily. Good feeling and high spirits are in the air. You can't feel downhearted when you breathe the city's bracing sea-tang and see its hill rising in the sparkling sun above the blue Bay.

For scenic beauty, few places in the world can excel San Francisco itself.

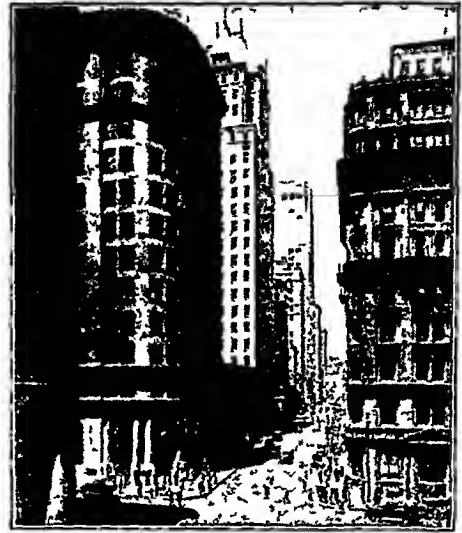


Fisherman's Wharf

A tour of the city can be made as exciting and as filled with surprises as a first visit to some picturesque foreign town. The Presidio military reservation, founded by the Spanish in 1776, is one of the largest and most beautiful army posts in the country. Golden Gate Park is known around the world. The Ocean Beach and the Cliff House with its seal rocks, the public golf courses of Lincoln Park overlooking the Golden Gate, the eminences of Russian and Telegraph Hills, the quaint cable cars on the steeper streets, the picturesque foreign quarters, the glowing flower stands lining the curbs in the shopping district—all of these provide endless entertainment and diversion.

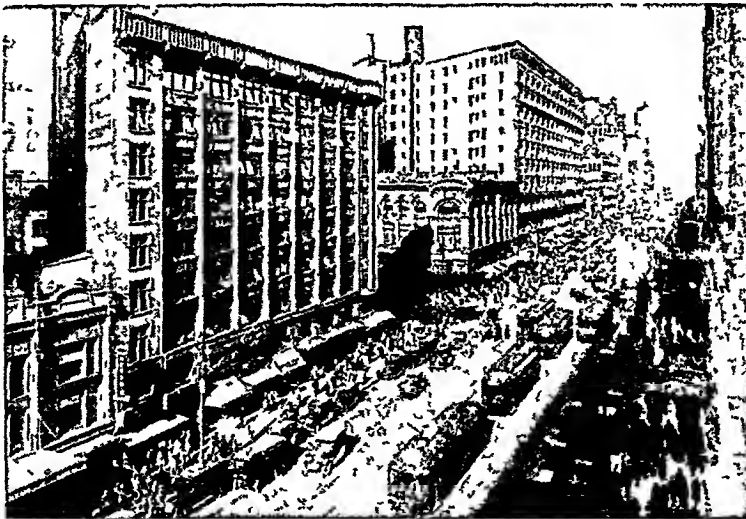
LURE OF THE SHIPS

Business and cultural metropolis of the Pacific Coast, San Francisco is first of all a great sea-port. In scenic grandeur, its great land-locked harbor ranks with Rio, Naples, and Constanti-



Montgomery Street, San Francisco

nople. To visit the waterfront, only a few minutes from the hotel and business section, is to feel one's self in touch with many strange far-off lands. You will see ships arrive and depart from Asia and the South Seas, for Latin America and Europe. You will hear strange tongues, see strange faces, smell the spice and fruits of the trop-



Market Street, San Francisco



Giant Redwoods in Muir Woods

ics, watch endless bales of raw silk swung from the hold of a great trans-Pacific liner. San Francisco is the gateway to the Hawaiian Islands, with frequent sailings via famous *de luxe* liners. San Francisco is the center from which American travelers, American ideas, and American goods are

carried to the hundreds of millions of awakening peoples inhabiting the great Pacific basin. Here the Orient and South Seas discharge their treasures. On these docks spill copra from the South Sea and Philippines, silks and teas from Japan and China, coffee and bananas from Central America, peasant ware from Spain and Italy.

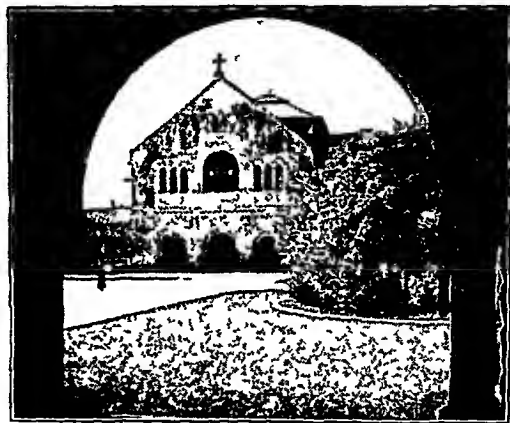
PACIFIC AREA'S TREASURE-HOUSE OF ART

For eighty years the people of the Western Slope and of the Pacific Islands have looked to San Francisco for entertainment and instruction. Today traveling Europeans are amazed by the treasures of its galleries, the excellence of its great orchestra, the vitality and stir of its cultural life. The Palace of the Legion of Honor, a



Mission Dolores, founded 1776

beautiful white marble replica of the famous Paris original, occupying a magnificent site commanding the Golden Gate and the open Pacific, holds priceless collections. So does the M. H. deYoung Memorial Museum in Golden Gate Park, and the beautiful California School of Fine Arts on Russian Hill. San Francisco has always been beloved by the stage, and its many theatres offer a variety of fare throughout the year.



Memorial Chapel at Stanford University

YOU CAN GOLF, FISH OR SWIM

Within twenty minutes of your hotel are golf courses where Bobby Jones could drive a ball from a putting-green high on the cliff right into the Pacific Ocean. Not even old Edinburgh has such a setting for its national game. You will be welcomed to the city's finest courses. Perhaps you would rather board a sturdy launch and fish for sea-bass or salmon in the Bay, or outside

the Heads in the open Pacific. It is easily arranged. So is trout-fishing in the Sierra or Coast-Range streams. For swimmers, there are the ocean beach, the famous in-door Sutro baths, and the Fleishhacker municipal open-air pool, the largest in the world.

YOU'LL FEEL AT HOME

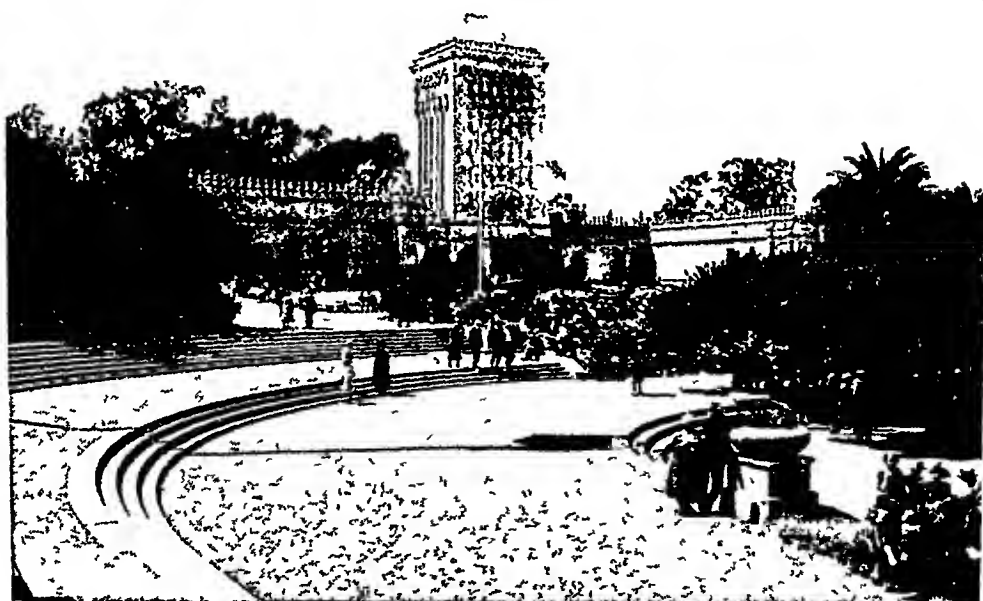
The City is a paradise for those who enjoy good food. There are lit-



Memorial Stadium at University of California, Berkeley



Lincoln Park Municipal Golf Course overlooking the Golden Gate



DeYoung Memorial Museum, Golden Gate Park

erally thousands of restaurants and their rates are surprisingly low. Food is important in San Francisco. Restaurateurs are artists as well as business men. Many are well-loved town characters. You feel the difference. And you like the friendliness. It's a happy town. Around the corner from the big hotels are Italian and French restaurants famous for a soup, a salad, a specially-prepared sea-food served with care and pride at low prices. You can dine in China, Russia, Japan, Sweden, France, Spain, Italy or Germany by merely calling a taxi or walking a few blocks through streets rich in reminders that this is a great cosmopolitan sea-port. For five cents you ride to the Beach, and lunch or dine with surf pounding outside and nothing

between you and Asia except the Pacific and a few islands. Or you can mount Telegraph Hill, rising steep between the docks and the Latin Quarter, and sit at tables commanding a superb expanse of blue salt water and encircling mountains. San Franciscans themselves like to go to Fisherman's Wharf, where the Madonna-blue boats bob with the tide, and dine in Italy on fresh-caught sea-food. The Bay, the Golden Gate, and Mt. Tamalpais look on you there.

CHINATOWN

San Francisco's Chinatown is world famous. Here are more dazzling displays of objects of art, silks, china and curious knick-knacks than are to be found in cities of China itself. Here



San Francisco's world famed Chinatown

also are the two largest Chinese theaters outside of China, playing the weird dramas of Cathay with Chinese orchestras and every touch complete

SAN FRANCISCO'S DISTINCTIVE CLIMATE

In the summer it is America's coolest city—the warm California sun tempered by sea breezes and an opalescent reminder of sea mist which often takes the form, toward evening, of billowing white fog bringing the breath of the sea. Yet no circumstantial description of San Francisco can account for its peculiar appeal to the

visitor without taking into account a certain atmosphere of romance and charm that is instantly felt and that proves invariably winning to the stranger. It is compounded of the unusual physical setting and climate, of the happy, healthy people, of the high hills and stunning vistas, of the foreign settlements and the oriental flavor, and also of a long tradition of stirring and romantic days, from the Spanish down through the Forty-niners to the bonanza kings of the Comstock Lode, the builders of our first transcontinental railroad, and the more recent generation that built a great modern city on the ruins of the old.



Mt. Tamalpais

Abstracts

A Study of 503 Cases of Pulmonary Tuberculosis with Indefinite or No Usual Abnormal Physical Signs By LAWRASON BROWN (Am Jr Med Sci, 1931, clxxvii, 700-707)

"As far back as the beginning of the century, Osler, among others, recognized that extensive disease of the lungs could exist with few or no abnormal physical signs

I wish to present to you some conclusions I have arrived at from a study of some 503 such cases selected from 1900 consecutive cases at the Trudeau Sanatorium

The method by which a diagnosis of chronic pulmonary tuberculosis was established in these cases is that used for some years at the Trudeau Sanatorium The occurrence alone of either hemoptysis of a drachm or more, or of pleurisy with effusion, explainable on no other grounds, is considered to justify a diagnosis of suspected pulmonary tuberculosis in the absence of all other symptoms

The occurrence of moderately coarse râles or of a parenchymatous roentgen ray lesion (mottling, irregularly distributed) above the third rib and third vertebral spine was considered sufficient evidence for a positive diagnosis of pulmonary tuberculosis until disproved Tubercle bacilli in the sputum in the absence of lesions above the trachea must be considered as absolute proof of pulmonary tuberculosis The incidence of these five cardinal diagnostic data in 1367 cases diagnosed pulmonary tuberculosis from 1478 consecutive cases admitted to the Trudeau Sanatorium is as follows

	<i>Per cent</i>
Tubercle bacilli	61 5
Râles	68 5
Roentgen ray	99 0
Hemoptysis	33 5
Pleurisy	12 0

From the data here presented I am inclined to attribute considerable importance

in the diagnosis of pulmonary tuberculosis to the roentgen ray examination I am convinced it will reveal the lesions of the disease long before it is manifested in any other way "

Vioosterol Treatment in Experimental Hyperparathyroidism By HENRY L JATTE AARON BODANSKY and JOHN E BLAIR (Proc Soc for Exp Biol and Med, 1931, lxxix, 207-208)

Three groups of experimental animals (guinea pigs) were established To those in the first group viosterol was given daily for 7 to 10 days After this preliminary treatment, the animals were injected daily with parathormone in increasing amounts, and the viosterol was also continued This combined medication extended over a period of 23 days In a second group viosterol and parathormone were started simultaneously and administration extended over a period of 29 days The third group contained 6 controls which were injected with parathormone as in the second group, but these animals did not receive viosterol The animals in all three groups were killed to terminate the experiment and their bones were taken for histological examination They all showed decalcification and secondary fibrous invasion of the bones There was no consistent difference in the nature or severity of the lesions between the guinea pigs receiving viosterol and parathormone (groups 1 and 2) and those receiving only parathormone Under the conditions of this experiment irradiated ergosterol did not protect from the demineralizing effects of experimental hyperparathyroidism It is possible, however that the healing of bone lesions in experimental or clinical hyperparathyroidism might be promoted by viosterol after the state of hyperparathyroidism had been terminated by discontinuance of parathormone administration, or by the removal of a parathyroid adenoma

Nonsyphilitic Aortic Valve Deformity By B J CLAWSON (Arch Path, 1931, vii, 889-899)

Nonsyphilitic aortic valve disease is of two kinds active vegetative endocarditis, and deformity due to thickening and roughening with scar tissue and often with calcium deposits. The frequency, and particularly the etiology, of the latter type have been subjects of much discussion in the last few years. The author's series contains 93 cases of aortic valve deformity of the calcified nodular type. In 91 per cent of 68 cases in which this point was investigated, some degree of stenosis was present. It is evident that aortic stenosis of a grade recognizable clinically, and due to this type of valvular deformity, is far more rare. Both gross and microscopical findings in these valves tend to support the view that the etiological factor is an inflammatory rather than a metabolic (atherosclerotic) condition. The frequency of rheumatism in these cases, as indicated by a previous positive history, by the presence of an adherent pericardium or by an association of deformities in other valves, strongly supports the view of an infectious basis. It is doubtful whether a valve deformity severe enough to cause cardiac insufficiency is ever due to a metabolic disturbance such as arteriosclerosis. Accordingly the term 'arteriosclerosis valve deformity' should not be used in describing valvular insufficiency or stenosis.

Effect of Giving Digitalis on the Volume Output of the Heart and its Size in Heart Failure By HAROLD J STEWART (Proc Soc for Exp Biol and Med, 1931, xxi, 207-208)

The method of Grollmann for measuring the cardiac output was utilized in studying the effect of digitalis on the heart of normal individuals. Digitan (Merck) was given in a single dose of 0.8 gm to 1.0 gm. Observations were made immediately before the drug was given and at frequent intervals afterward. All observations were made with the subjects in a basal metabolic state. In addition to measurements of cardiac output, the cardiac size was measured on x-ray photographs made at a distance of two meters. Electrocardiograms were made also,

the heart rate was counted and the blood pressure recorded. Consistent results were obtained from the four subjects studied. With the administration of digitalis to normal men (1) cardiac output *decreased*, (2) the cardiac size *decreased*, (3) the cardiac rate *decreased*, (4) alterations of the T-wave of the electrocardiogram occurred, (5) the blood pressure was usually elevated, (6) the maximum effects were observed 9 to 24 hours after the drug had been given, and had usually passed off at the end of 48 hours.

Effect of Giving Digitalis on the Volume Output of the Heart and its Size in Heart Failure By HAROLD J STEWART (Proc Soc for Exp Biol and Med, 1931, xxi, 209-211)

The methods referred to in the preceding abstract were used in a study of the effect of digitalis on the volume output and size of the heart in heart failure. A small group of patients, among whom were included examples of arteriosclerotic, luetic and rheumatic heart disease, with and without disturbances of rhythm, gave results indicating that in the presence of heart failure (1) the cardiac output diminishes. (2) With the administration of digitalis (a) the cardiac output increases, (b) the cardiac size diminishes, (c) the ventricular rate decreases both when the rhythm is normal and in the presence of auricular fibrillation, (d) and alterations in the form of the T-wave of the electrocardiogram occur. (3) As the effect of digitalis wears off, these functions change in the reverse direction.

Tularemic Leptomeningitis By ARTHUR R BRYANT and EDWIN F HIRSCH (Arch Path, 1931, xii, 917-923)

A chef, aged 48, died on the sixteenth day after lacerating a finger with a rabbit bone while removing pickled rabbit from a jar. At autopsy focal lesions were found in the leptomeninges, contiguous brain tissues, ependyma, subependymal tissues and choroid plexus, which were similar to lesions in the liver, spleen and lungs. All of these had the characteristics of tularemic lesions. In addition there was a diffuse acute exudative meningitis. The serum of the patient, taken

on the fourteenth day, was reported to agglutinate *Bacterium tularensis* in dilutions not greater than 1:40. This low titer is not considered to militate against the diagnosis of tularemia when the serum was taken as early as the fourteenth day from a patient whose failure to form antibodies was indicated by his death two days later. Differentiation from military tuberculosis was made

possible in that suspensions of the crushed lesions killed guinea pigs in five days and produced in them visceral lesions characteristic of tularemia, staining for tubercle bacilli gave only negative results, and lesions of a frankly tuberculous character were not found in the course of a thorough gross and histologic examination of the viscera of the patient.

Reviews

Medical Jurisprudence. By CARL SCHEFFEL, Ph.D., M.D., LL.B. xii + 313 pages. P. Blakiston's Son and Company, Inc., Philadelphia, 1931. Price, \$2.50, postpaid.

Contrary to the procedure of most writers on this subject, Scheffel treats of the effect of law upon medical practice and practitioners rather than the reverse. The material presented is of a general character so that the book should be of service to the entire medical profession. There is no attempt to impart highly specialized knowledge applicable only to restricted medical groups. The major divisions of law as they affect the physician are discussed with particular emphasis upon what the author chooses to term "legal prophylaxis", that is, the prevention of unfortunate legal complications involving the medical practitioner. The subjects treated include contractual relationships, law of agency, torts or civil wrongs other than breach of contract, principles of evidence, function of the medical witness, property interests of physicians, criminal responsibility and physicians as law makers. Much of value to the average practitioner is contained in the chapters on contracts and agency. The types of contracts occurring in medical practice, and the specific liabilities of physician and patient in each are well illustrated with specific examples, and many practical suggestions are made to aid in avoiding unnecessary liability. There is included an exposition of various types of commercial contracts which the medical man is especially prone to make, oftentimes unwittingly, herein is timely and practical advice which should be invaluable. The function of the physician

in court is developed at length and an effort is made to show how this relationship affects both the process of justice and the physician himself. The rights of the witness, expert and otherwise, are outlined from the legal point of view, and the importance of an adequate comprehension of the strict meaning of terms commonly used in court is stressed. In general it may be said that the book reflects a legal training rather than a medical one, that it deals with the lawyer's view of the physician rather than with the latter's evaluation of his problems of law and social responsibility. This is particularly evident in the section dealing with autopsies wherein attention is called to a supposed disadvantage of the autopsy because it is thereby frequently shown that the clinical diagnosis was erroneous and that treatment had been applied for a condition that did not exist, thus the liability for malpractice suits may be increased. If such fears were to dominate the medical profession, then progress in scientific medicine would be practically nil. The emphasis on this aspect of the autopsy seems peculiarly ill-advised. Notwithstanding such points which may be called in question, this attitude of mind on the part of the author is in keeping with the purpose of the book and is undoubtedly a large factor in making the work of greater personal value to members of the medical profession than many similar publications. The manuscript is well organized, the argument is logical, the style vivid, only numerous typographical errors and the rather frequent use of a plural pronoun with a singular antecedent mar an otherwise artistically compiled treatise.

Clinical Dietetics A Textbook for Physicians, Students and Dietitians By HARRY GAUSS, M S, M D, F A C P, Instructor in Medicine, University of Colorado, School of Medicine, Assisted by E V GAUSS, B A, Formerly Assistant Dietitian, Presbyterian Hospital, Denver, Colorado 490 pages, 59 illustrations The C V Mosby Co, St Louis, Mo, 1931 Price \$8.00

The needs of three distinct groups, students of dietetics, medical students, and practitioners, were kept in mind as this textbook was being written. Certain difficulties are inherent in the attempt to present the subject matter of use to each of these groups without becoming tiresome to the others. Yet the authors seem to have succeeded to an unusual degree. The first four chapters give a brief but interesting historical outline, a survey of the nature of foods, of dietetic principles, and of the theory of digestion. The latter half of the book is concerned with clinical applications of dietetic principles. A few minor flaws—at least they appear to be such to the reviewer—can be easily remedied in a second edition. It is unfortunate that vitamin E is made to include the pernicious anemia preventing principle, as well as the anti-sterility factor to which this letter should be restricted. Although the fact that both glomeruli and tubules frequently share in nephritis is clearly set forth in the text, the use of Richard Bauer's super-simplified diagram is unfortunate. There are also a number of small but important typographical errors which need correction. The use of historical material is skillfully managed and the introduction of case histories in smaller type adds much to the clinical interest and value. It is encouraging to those who stress in their teaching the importance of constitution, in the sense of Pyle, to find that no less than 16 pages are given over to the significance

A Manual of Clinical Laboratory Methods By CLYDE LOTTRIDGE CUMMER, Ph B, M D, F A C P., formerly Associate Clinical Professor of Clinical Pathology, School of Medicine, Western Reserve University, Cleveland, Instructor in Dermatology and Syphilology, School of Medicine, Western Reserve University, Visiting Dermatologist, Charity and St Alexis Hospitals, Cleveland, Ohio Third Edition, thoroughly revised 585 pages, illustrated with 173 engravings and 12 plates Lea and Febiger, Philadelphia, 1931. Price \$6.75, net

This manual of laboratory methods should be of value to the medical practitioner, as well as to the laboratory technician, because of its style of presentation, which, though concise, gives minute details of even simple procedures. The book consists of twelve chapters, the first five of which deal with the blood, its examination, differential diagnosis of blood dyscrasias, parasitology and bacteriology of the blood, immunology and blood chemistry. An appendix gives an efficient method for examining a large number of urine specimens in a hospital laboratory. This portion of the book also takes up the preparation of normal solutions, the preparation of stains and of autogenous vaccines, as well as other information of interest and value. The last two pages of the book are made up of a Table of Normal Findings, which will be appreciated particularly for the more unusual laboratory procedures. The author presents the newer tests as well as the recent modifications of the standard methods. He describes Kline's Macroscopic Slide Test for syphilis, commenting briefly upon its value. The charts and illustrations are, on the whole, very good and a distinct addition. A bibliography requiring 19 pages gives citations to the original articles in which the technical methods now in vogue were described.

Febiger, Philadelphia, 1931 Price, \$6.50 net

For this second edition of *Hypertension and Nephritis* the entire book had to be reset, so extensive was the revision. The sections on renal acidosis, azotemia with chloride deficiency, the Addis ratio, the pathogenesis of edema, the kidney in diabetes and hemoglobinemia, the role of sensitization in glomerulo-nephritis, renal osteo-dystrophy, the carotid sinus and regulation of blood pressure, cardiac failure in hypertension, and paroxysmal hypertension with suprarenal tumors are either new or have been rewritten. As a result, in this edition the number of pages has been increased by about 50. This is a very complete and satisfactory discussion of the subject, written with the needs of the general practitioner especially in mind. The simpler methods of clinical investigation are stressed and their value emphasized. Throughout management and treatment are set forth in connection with the discussion of each clinical group. This practical clinical application does not mean that the method suffers from lack of scientific analysis, for both morphological pathology and altered physiology are thoroughly presented. Not all pathologists will agree with the elimination of the tubular system from the conception of a defensive nephritis, but approval will be general for the elimination of the term chronic interstitial nephritis, and the firm stand that there is no justification for its use "as commonly applied to those renal diseases which are characterized clinically by arterial hypertension and its consequences."

A Text-Book of Pathology By FRANCIS DELAFIELD, M.D., LL.D., sometime Professor of the Practice of Medicine, College of Physicians and Surgeons, Columbia University, New York City, and T. MITCHELL PRUDDEN, M.D., LL.D., sometime Professor of Pathology, College of Physicians and Surgeons, Columbia University, New York City. Fifteenth edition, revised by FRANCIS CARTER WOOD, M.D., Director of the Pathological Department, St. Luke's Hospital, New York, Director of the Institute of Cancer Research, Columbia University, New York. 1339 pages, 20 full-page plates, 830 text illustrations. William Wood and Company, New York City, 1931. Price, \$10.00.

No extended review of this well and favorably known textbook is needed. The present edition, the fifteenth, appears after an interval of four years during which time many notable advances in the field of general pathology have been made. Those additions which appear significant and lasting have been added in the revision. The task of including within one book the essentials of both general and special pathology grows more difficult of accomplishment with each succeeding year. Detailed treatment of any one field under such circumstances has become entirely impossible. This well-balanced text continues to be one of the most satisfactory sources for the fundamentals of pathology to be found in the English language. The addition of references to recent reviews directs the reader to more extended information. Many more citations could have been made to advantage.

College News Notes

Acknowledgement is made of the receipt of gifts to the College Library of publications by members, as follows:

Dr Clarence L. Andrews (Fellow), Atlantic City, N. J.—1 book, "How's your blood pressure",

Dr William W. Cadbury (Fellow), Canton, China—5 reprints,

Dr Nathan S. Davis, III (Fellow), Chicago, Ill.—4 reprints,

Dr George H. Lathrope (Fellow), Newark, N. J.—8 reprints,

Dr Eugene P. Marzullo (Associate), Brooklyn, N. Y.—1 reprint,

Dr Aaron E. Parsonnet (Fellow), Newark, N. J.—1 reprint,

Dr Martin J. Synnott (Fellow), Montclair, N. J.—1 reprint,

Dr. Fritz B. Talbot (Fellow), Boston, Mass.—1 reprint,

Thorndike Memorial Laboratory, Boston, Mass.—41 reprints

Dr Henry Daspi (Fellow), New Orleans, Louisiana, Dean of the Graduate School of Medicine of The Tulane University of Louisiana, participated November 23 and 24 in a Medical Institute at Rutherford Hospital, Murfreesboro, Tennessee, presenting papers entitled "Epidemic Encephalitis in General Practice" and "Preventive Medicine Aspects of Psychiatry", and giving a neuro-psychiatric clinic

Dr Harold F. Machlan (Fellow), has been transferred from the U. S. Veterans' Hospital, Lake City, Florida, to become Clinical Director of the U. S. Veterans' Administration Hospital at Indianapolis, Indiana

Dr Roy C. Mitchell (Fellow), Mount Airy, North Carolina, addressed the Grayson-Carroll County Medical Society of

Virginia, November 9, on the subject, "Indigestion After Forty"

Dr Wade W. Oliver (Fellow), Professor of Bacteriology in the Long Island College of Medicine, Brooklyn, N. Y., with his wife, recently returned from an eighteen months' trip around the world. Dr. Oliver was sent by the Rockefeller Foundation as Visiting Professor of Bacteriology and Immunology in the School of Hygiene and Public Health of the University of the Philippines, Manila. He served there during the teaching year of ten months from May, 1930, until March, 1931. The remaining eight months were spent in visiting bacteriological laboratories in, and touring Hawaii, Japan, Korea, China, Bali, Java, Federated Malay States, Siam, Burma, India, north Egypt, Italy, France and Germany

Dr Oliver T. Osborne (Fellow), New Haven, Conn., is the author of an article entitled, "Foods and Health", which appeared in the Illinois Dental Journal for November, 1931. Dr. Osborne is also the author of an article in the Stomatologic Record, New York City, September-October, 1931, entitled "My Viewpoint of Dentistry"

Dr Carl R. Howson (Fellow), of Los Angeles, California, was recently elected President of the Southern California Medical Association. Dr. Harry Henderson (Fellow), Santa Barbara, was elected First Vice President, and Dr. Robert Ramsay (Fellow), Pasadena, was elected Second Vice President. Dr. Fred B. Clarke (Fellow), Long Beach, was the retiring President

Dr H. Beckett Lang (Fellow), was recently appointed Director of Clinical

Psychiatry at the Marcy State Hospital, Marcy, Pennsylvania

Dr. Lang addressed the Fulton Medical Society, October 20, 1931, on "The Mental Hygiene Clinic in the Community" On the same date he also addressed the District Health Officers at Syracuse on "The Malarial Therapy in Neurosyphilis" On November 2, 1931, Dr. Lang addressed the Parent Teachers Association of Hamilton, New York, on "Behavior Problems and Their Relation to Mental Illness"

Dr. George L. Pinney (Fellow), Hastings, Nebraska, was recently elected Secretary and Treasurer of the Republican Valley Medical Society Dr. Pinney recently addressed the Nebraska State School Teachers Association on "Common Sense Pointers on Physical Education"

Dr. Clough Turrill Burnett (Fellow), Associate Professor of Medicine at the University of Colorado School of Medicine, delivered addresses at the Colorado State Medical Society in September, 1931, and at the Boulder County Medical Society in Longmont on November 12

Dr. George H. Hoxie (Fellow), Kansas City, Missouri, was elected President of the Missouri State Tuberculosis Association at its last meeting in St. Joseph, during October Dr. Hoxie is Medical Director of the Open Air Schools in Kansas City, as well as of the Kansas City Tuberculosis Society

The following Fellows of the College were on the program of the Tenth Annual Meeting of the Eastern Homeopathic Medical Association held at Trenton, New Jersey, November 4, 5, and 6 Dr. Donald R. Ferguson, Philadelphia, Dr. E. Roland Snader, Jr., Philadelphia, Dr. G. Harlan Wells, Philadelphia, Dr. Milton J. Raisbeck, New York, and Dr. Linn J. Boyd, New York

Dr. Lewis Jefferson Moorman (Fellow), Dean of the University of Oklahoma School of Medicine, Oklahoma City, is the President-Elect of the Southern Medical Association, having been elected at the recent meeting in New Orleans

Dr. Frank Smithies (Master), Chicago, was elected President of the American Society of Tropical Medicine at its Twenty-Third Annual Session, held at New Orleans, November 19, 1931

Dr. Albert E. Russell (Fellow), of the U. S. Public Health Service, Washington, D. C., delivered an address on Silicosis and Tuberculosis before the Milwaukee Academy of Medicine, Milwaukee, Wisconsin, on November 10, 1931 Dr. Russell also read a paper on Occupation and Respiratory Diseases before the Section on Public Health of the Southern Medical Association in New Orleans, November 20, 1931

Dr. Karl D. Figley (Fellow), Toledo, Ohio, presented a paper on "Food Allergy" before the Academy of Medicine of Toledo and Lucas County, November 6, 1931

Dr. Samuel M. Femberg (Fellow), Chicago, addressed the Rock Island County (Illinois) Medical Society on "Allergy in General Practice", December 8, 1931

Dr. Edgar Mayer (Fellow), Saranac Lake, New York, Associate Professor of Medicine, New York Post-Graduate Medical School and Instructor at the Trudeau School of Tuberculosis, was the guest speaker at a special meeting of the Pacific Physical Therapy Association, held at Los Angeles, December 9, 1931 Dr. Mayer's subject was "Are We Abusing our Patients with Light"

Dr. Henry M. Moses (Fellow), Brooklyn, New York, addressed the Medical Society of the County of Kings, November 17, 1931, on "Pulmonary Neoplasms—The Clinical Findings and Methods used in Diagnosis"

Dr. Franklin B. Bogart (Fellow), Chattanooga, Tennessee, read a paper before the Radiological Section of the Southern Medical Association, at New Orleans, in November, on the subject "X-Ray Examination of the Heart in Left Auricular Enlargement"

Dr Hyman I Goldstein (Associate), Camden, New Jersey, during September and October, 1931, addressed the Krankenkassa physicians in Vienna on "The Physician in American Life To-day—His Position, Socially, Economically, and Scientifically" He spoke on the subject of "Goldstein's Heredofamilial Angiomatosis with Hemorrhages", with lantern demonstration, before the Hungarian Dermatologic Society at Budapest, the Professor Baron A Korányi Medical Clinic, and the Professor Nékám Dermatologic Clinic of the Royal University, both at Budapest, before the German physicians of Carlsbad, Czecho-Slovakia, the American Medical Association, of Vienna, and also before the Professor Morawitz Medical Clinic, Leipzig University, Leipzig, Germany

Dr A L Anderson (Fellow), Springfield, Mo, on November 12, gave a paper before the Southwest Missouri Medical Society on "Metabolimetry as a Measure of Function in the Field of Clinical Medicine"

Dr Chas Hugh Neilson (Fellow), of St Louis spoke on the same program on "Newer Theories of Nephritis", and at the banquet of the Society responded to the toast, "Observation in Medical Education and Medical Practice"

Dr Sidney Alexander Slater (Fellow), Worthington, Minn, addressed the Southwestern Minnesota Medical Society at their semiannual meeting, October 6, 1931, on his recent tour of European clinics

On December 3, Dr Slater addressed the Sioux Valley Medical Society at its annual meeting on the same subject

The Eighty-Fifth Semi-Annual Meeting of the Southern California Medical Association was held in Hollywood, November 13 and 14, 1931, under the presidency of Dr Fred B Clarke (Fellow), Long Beach, Calif Other Fellows of the College who held offices were

Dr. William H Barrow, San Diego, Calif—First Vice President,

Dr Carl R Howson, Los Angeles, Calif—Secretary-Treasurer

At the above meeting, Dr. Ross Moore (Fellow), Los Angeles, delivered a paper

on "A Concept of Toxic Activity—Therapeutic Application", and Dr Samuel Ayres, Jr (Fellow), Los Angeles, in conjunction with Dr Nelson P Anderson, delivered an address on "The Use of the Patch Test in the Diagnosis of Contact Dermatitis"

Dr Clarence L Andrews (Fellow), Atlantic City, N J, was elected President of the Atlantic County (N J) Medical Society, December 11, 1931

Dr Arthur C Morgan (Fellow), Philadelphia, addressed the annual meeting of the Sixth District Branch of the Medical Society of the State of New York, at Waverly, N Y, September 22, 1931, on the subject "The Treatment of Acute Cardiac Tragedies".

Dr Fred H Voss (Fellow), Kingston, N Y, has been elected a member of the New York Academy of Medicine

On November 10, 1931, Dr George A Merrill (Fellow), Brooklyn, N Y, addressed the Bay Ridge Medical Society on the subject "Allergy and its Common Manifestations"

Dr. Ray M Balyeat (Fellow), Oklahoma City, Okla, Associate Professor of Medicine, University of Oklahoma Medical School, addressed The Medical and Surgical Association of the Southwest, at Phoenix, Arizona, December 4th on "History Taking and Etiology in Headaches Due to Specific Hypersensitiveness"

Dr Balyeat recently has been elected President of the Oklahoma City Clinical Society

At the Louisiana Follow-Up of the White House Conference on Child Health and Protection, November 12-14, at Baton Rouge, Dr Ellen C Potter (Fellow), Trenton, N J, conducted a round table on the "Functions of Government in Public Welfare", and addressed the general assembly on the responsibility of government in that field

In New Orleans, La, November 15-16, Dr Potter delivered addresses before the Branch of the Medical Women's National

Association and before the City Officials and Private Social Agencies concerning the "Interdependence of Public and Private Social Work"

Dr Potter addressed the Annual Convention of the New Jersey Organization for Public Health Nursing at Trenton, December 4, on "The Responsibility of Board Members" The same day, Dr Potter also addressed the State Conference of Social Work of New Jersey on "Community Organization for Social Work"

The Second District Branch of the Medical Society of the State of New York held its Twenty-fifth Annual Meeting at the St George Hotel, Brooklyn, November 19, 1931 Dr Henry M Moses (Fellow), Brooklyn, delivered an address on "Supportive Treatment of Pneumonia", Dr Albert F R Andresen (Fellow) and Dr Simon R Blatteis (Fellow), both of Brooklyn, delivered addresses on "Health Examination from the Standpoint of Gastro-enterology" and "Health Examination from the Standpoint of Internal Medicine", respectively

Dr Joseph H Barach (Fellow), Pittsburgh, Pa, addressed the Westmoreland County Medical Society, November meeting at Mount Pleasant, Pa, on "Treatment of Pneumonia"

Dr Robert A Knox and Dr George W Ramsey (Fellows), Washington, Pa, presented a case of Niemann-Pick's disease before the Pittsburgh Pediatric Society, October 23 This case will be described in a paper which has been accepted for a future number of the ANNALS

Dr Fred M Meixner (Fellow), Peoria, Ill, is the author of an article on "Chest Injuries as the Cause of Heart Lesions" in the December issue of the Illinois Medical Journal

Dr M Murray Peshkin (Fellow), New York City, addressed the Hackensack Hospital Staff Association, Hackensack, N J, Dec 15, 1931, on "Allergy in Children"

OBITUARIES

DR EDWARD TYLER EDGERLY

Dr Edward Tyler Edgerly, Fellow of the College since March 10, 1925, died in Rochester, Minn, on November 15, 1931, following an operation for vesical calculus, at the age of sixty-seven years

Doctor Edgerly was born in Ottumwa, Iowa, January 15, 1864 After attending the Ottumwa public schools he graduated from Phillips Exeter Academy and received his A B degree at Harvard University in 1885 He graduated in medicine from Northwestern University Medical School in 1889 In the competitive intern examination for Cook County Hospital, Chicago, he received the highest grade and became chief of the resident intern

staff After completion of his intern service, he was appointed an instructor in medicine and physical diagnosis of his Alma Mater

In 1894, while on a tour of European medical centers accompanied by his father, Mr J W Edgerly, the latter died suddenly in Paris, and this unfortunate occurrence changed the course of Doctor Edgerly's career In the interest of the family fortunes, Doctor Edgerly made the willing sacrifice of a promising medical future in Chicago and devoted his services to the business interests of the family until 1908, when he returned to his old love and began the active practice of medicine in his home city His fine training and high mental endowments

soon brought him into leadership among the physicians of his state

In 1902 he was commissioned First Lieutenant in the Medical Reserve Corps, U. S. Army, and entered active service at the beginning of the World War. He served as Captain and Major, and Chief of the Medical Service of the Base Hospital at Camp Dodge during the period of the War. During Major Edgerly's service at Camp Dodge his conduct of the epidemics of meningitis and influenza received official commendation.

He was a member of the Wapello County and Iowa State Medical Societies, the Iowa Clinical Medical Society (past president), and the American Medical Association. He was an active member of the Iowa Tuberculosis and the Iowa Heart Associations.

Doctor Edgerly was married in 1891 to Miss Nettie Thurston of Chicago, who with a son, John T. Edgerly, and a daughter, Mrs. Nelson Rupe, and four grandchildren survive.

Since his affiliation with the College he has been an active worker in promoting its interests in every way and a faithful attendant at the annual meetings. During the Boston session in 1929 the members of his Harvard class (L. A. '85) arranged a dinner in his honor, and it was the writer's privilege to be present as a guest. Among those attending the dinner were Mr. Roland W. Boyden, eminent authority on international law and later successor to Justice Charles H. Hughes on the Court at the Hague; his brother, Mr. Wm. W. Boyden, a leading member of the Chicago Bar; Dr. Horace D. Arnold of Boston, a president of one of the leading life insur-

ance companies, and others prominent in the professions and public affairs. Greetings were read from Dr. W. S. Thayer of Baltimore, and Associate Justice Edward T. Sanford of the U. S. Supreme Court. The late Dr. Lawrence Litchfield of Pittsburgh was also a member of this class.

Doctor Edgerly distinctly contributed to the progress of scientific medicine during his period, and the impression of his fine and genial personality, generous nature, and high professional ideals will linger with us while memory lasts.

(Furnished by Walter L. Bierring, M.D., F.A.C.P., Des Moines, Iowa)

DR. JOHN FRANCIS WALLACE MEAGHER

Dr. John Francis Wallace Meagher (Fellow), Brooklyn, New York, died August 25, 1931, of injuries received when a concrete pillar supporting an observation platform on which he was standing collapsed. He was fifty-one years old and in the prime of health and vigor.

Dr. Meagher was born in Brooklyn, March 22, 1880. He was graduated from the Boys High School of Brooklyn and from the College of Physicians and Surgeons of Columbia University in 1901. He was an intern at St. Mary's Hospital, Brooklyn, from 1901 to 1902. In 1903 he made a special study of nervous and mental diseases at St. Lawrence State Hospital, Ogdensburg, New York, and later at the Manhattan State Hospital for the Insane at Ward's Island, New York. Thereafter he was associated in this work at the Bellevue Psychopathic Ward and in the Neurological Insti-

tute During the World War he served in the rank of major At first he was stationed at Camp Mills, Mineola, and later at Kelly Field, San Antonio He was sent overseas and worked at Base Hospital 37, Dartford, Kent, and after that at Base Hospital 216 at Savenay, France After the war was over he remained in the service in the capacity of psychiatrist at the Army Hospital at Plattsburg, New York, and was discharged in 1919

At the time of his death, Dr Meagher was Consultant Psychiatrist at Kings Park State Hospital and Neurologist at St Mary's, Mary Immaculate, and Rockaway Beach Hospitals

Dr Meagher was a frequent contributor to medical literature and was associate editor of the Medico-Legal Journal and associate editor of the Journal of Urology and Cutaneous Diseases His special interest, however, was in the legal and criminal aspects of mental abnormalities and diseases For many years he had been a consultant alienist in the office of the District Attorney of Brooklyn, where his talents and abilities, along his special lines, were recognized as invaluable to the solution of their problems

He was a member of the Pi Lambda Phi and the Chi Zeta Chi Fraternities He was a member of the American Medical Association, New York Academy of Medicine, Neurological Society of New York, Neurological Society of Brooklyn, American Psychiatric Association, Medical Society of the County of Kings, and the Society of Medical Jurisprudence He was also a member of the Crescent

Athletic Club and the Cavalry Club of Brooklyn He became a Fellow of the American College of Physicians in 1920

(Furnished by Luther F Warren, M D, F A C P, Governor of Eastern New York)

DR LAWRENCE EVANS CHAPMAN

Dr Lawrence Evans Chapman (Internal Medicine) was born August 28, 1887, at Georgetown, Texas, received his M D degree from the University of Texas, School of Medicine, 1915, and became a member of the Galveston County Medical Society, the South Texas District Medical Society, State Medical Association of Texas, Southern Medical Association and American Medical Association He was elected a Fellow of the American College of Physicians, March 4, 1928 At the time of his death Dr Chapman was Associate Professor of Clinical Medicine at the University of Texas School of Medicine, and a visiting physician on the staff of the John Sealy Hospital He died suddenly, October 21, of coronary thrombosis

Dr Chapman was a man of the highest principles, of the utmost devotion to the teaching and practice of Internal Medicine, and a most excellent type of gentleman His death came as a great loss to the Medical Department of the University of Texas, with which he had been associated in various positions since 1915 He first became associated with the faculty as Instructor in Physiology, which position he held until 1917 After his training in Physiology, he became connected with the Chair of Practice of

Medicine where he continued until his death, passing through successive and rapid promotions from Instructor to the rank of Associate Professor

(Furnished by C T Stone, M D ,
F A C P , Governor for Texas)

DR THOMPSON FRAZER

Dr Thompson Frazer (Fellow), Newark, New Jersey, died suddenly October 9, 1931, of cerebral hemorrhage, aged fifty-four years

Dr Frazer was born in Buffalo, New York, September 10, 1877 He attended the Newark Academy of Newark, New Jersey, and later Princeton University, from which he received the degree of B S in 1897, and M S in 1904 He received his medical training at the College of Physi-

cians and Surgeons at Columbia University, receiving his medical degree in 1901

Dr Frazer practised medicine in Asheville, North Carolina, for some time, later removing to Newark, New Jersey, where he established himself Among his appointments was that of Visiting Physician, St Barnabas Hospital He was a member of his county and state societies, Southern Medical Association, The American Heart Association, American Climatological and Clinical Association, and a Fellow of the American Medical Association He was elected an Associate of the American College of Physicians on March 13, 1925, and his credentials for Fellowship were accepted on December 30, 1926

Multiple Arterial Occlusions*

By HAROLD W. DANA, M.D., F.A.C.P., *Boston, Mass.*

FOR many years we have been cautioned, with regard to the use of quinidine in the treatment of auricular fibrillation, of the possible danger that we might cause the extrusion into the circulation, when the previously dilated auricles should contract, of thrombi formed in these inactive chambers of the heart. Such an accident would seem not only to be possible, but even to be likely, should any method of treatment be successful in re-establishing rhythmic contraction of auricles long inactive, and undoubtedly this misfortune does at times follow the use of this drug, although much less frequently than one would expect upon theoretical grounds.

Outside of the cinchona group, no drug is known to have an effect on auricular contraction. Digitalis, though widely used in fibrillation, is employed only as a means of setting up a barrier against ventricular overstimulation. Mackenzie¹ in speaking of the danger from the use of digitalis in fibrillation, was referring only to the possibility of producing too great a degree of block after the pulse rate had become sufficiently slow. Hare² refers to the possible dangers of massive doses of digitalis in patients with a tendency to embolism "arising in all probability from the valvular disease",

apparently quite apart from any discussion of the effect of this drug in fibrillation.

In this paper I should like to present the hypothesis that pituitrin, either alone or in conjunction with adrenalin or digitalis, may be capable of causing the stationary auricles to contract rhythmically. The evidence is based upon the apparent effect of one or more of these drugs in causing what I believe to have been multiple embolism, with the simultaneous disappearance of a pre-existing fibrillation of the auricles. The patient in whom this occurred was, on this particular admission to hospital, under treatment for lobar pneumonia, and after having been digitalized, she had received repeated subcutaneous injections of pituitrin because of circulatory failure as evidenced by falling systolic and pulse pressures. She had also received one or more injections of adrenalin during one, at least, of the two severe chills with partial collapse following each of two large intravenous injections of glucose. There was no evidence of an endocarditis. No quinine had been used in treatment.

The effect of pituitary extract upon unstriated muscle, in the uterus, the intestine, and the blood vessels, is long established, within recent years

*Submitted for publication, June 9, 1931

several observers^{3,4} have noted the emptying of the gall bladder as the result of the action of this agent, and since cardiac muscle is closely related to unstriated involuntary muscle, it would seem at least theoretically possible to obtain some contractile influence upon the heart from pituitrin, which Dale⁵ believes does in fact occur. Twenty years ago, however, Wiggers,⁶ in a series of experiments both on the perfused heart and by intravenous injection, found that pituitrin did not cause any increase in the amplitude of cardiac contraction. More recent experimenters, as Ross with others⁷, Kolls and Geiling⁸, Geiling and Resnik⁹, speak of the possibility of direct action of the extract on heart muscle, or of indirect action through coronary constriction, though rather in causing dilatation than increased contraction.

It would seem that the only possible explanations for what occurred in the patient referred to, are as follows

(1) that the fibrillation was due to the pneumonia and disappeared when the patient's condition improved,

(2) that there was a spontaneous cessation of a paroxysmal fibrillation, and

- (a) that emboli were thereby extruded into the circulation, or
- (b) that thromboses occurred in various locations, also spontaneously, or
- (c) that the thromboses were due to the effect of pituitrin locally in causing narrow-

ing of the capillary bed in the extremities,

(3) that both the return to normal auricular rhythm and the occurrence of embolism were due either to pituitrin or to its effect combined with that of other drugs. Whether such possible effect of pituitrin might have been through stimulating the contraction of the auricles or through its depressant effect upon cardiac muscle, or by stimulation of the cardio-inhibitory center, will not be discussed.

Why glucose injections, when given in pneumonia, should produce, at times, a condition simulating anaphylactic shock, has not as yet been satisfactorily explained. It is possible that such a reaction may be due to massive destruction of leucocytes with the production of toxic substances. That either glucose shock or the single injection of adrenalin used in its treatment could have caused thrombosis in this case does not seem likely, since there was an interval of six days between the last use of these agents and the appearance of any arterial occlusion.

That fibrillation may have resulted from the pneumonia has no particular bearing, since there had been undoubted previous attacks of fibrillation. In fact, there is no actual proof that a spontaneous termination of fibrillation did not occur in this case. While the patient had had "palpitation of the heart" for eight or ten years and definite symptoms of cardiac decompensation for three years, when admitted to hospital one year ago with a diagnosis of auricular fibrillation, the heart action was reported as regular in all examinations during her three

weeks' stay, and no fibrillation was diagnosed at that time. However, no electrocardiographic examination was then made, for some reason, so that fibrillation with regular ventricular action cannot be positively excluded.

If, during the patient's latest stay in hospital, there had been a spontaneous restoration to normal rhythm, then the fibrillation can be assumed to have been paroxysmal in type, of short duration, unlikely to have produced clot formation and extrusion of emboli.

With regard to the possibility that there could have been a spontaneous re-initiation of auricular dynamic contraction, with an almost simultaneous onset of widely scattered thrombus formation due to the local action of pituitrin upon the blood vessels, there are the following difficulties to be ex-

plained. In the first place, this requires belief in a most remarkable coincidence, further, the vessels involved in the hands and feet were not merely capillaries, but vessels of good size, again, the first evidence of the process occurred in the tip of the nose, then in both feet, next in the right hand, later on the left forearm, probably in the lungs, and finally on one cheek, this distribution of lesions being spread over several days, and as a final argument, the process in the cheek seemed rather definitely embolic in that there was pus formation.

Unfortunately, the evidence in the case is not at all complete, for various reasons, chiefly mechanical, no electrocardiogram was taken until after the heart action had become regular, and eight days after the first evidence



FIG 1 Photograph of right hand, taken Feb 15th, 1931, showing condition of fingers at the time of discharge from hospital

of interference with peripheral circulation. Further, while it is the impression of several of us that the return to normal rhythm occurred at the same time that onset of gangrene of the extremities appeared, this cannot be substantiated from the hospital records.

Very much to the point is the observation of Halsey¹⁰ in Barker's Endocrinology. Rénon and Delille are quoted by Halsey as stating that arrhythmias were not influenced by pituitrin, but that in several cases tachycardia was controlled after other therapy had failed, and to this Halsey makes the commentary, "Every clinician of sufficient experience is aware of the difficulty of determining whether the cessation of one of these

paroxysms following any line of treatment is an instance of *post hoc* or *propter hoc*. However, there is pharmacological evidence that the injection of extracts of this gland may directly depress cardiac muscle and in this way it is possible that such would exert a favorable influence in tachycardia."

Resnik and Geiling¹¹ made an electrocardiographic study of the action of pituitary extract and showed changes in the heart rate, partly due to stimulation of the cardio-inhibitory centre and partly to a "muscular action". It is possible that the low amplitude of all waves in the earliest electrocardiogram from the case here reported is due to the depressant action of pituitrin, rather than to any specific action in making the auricles contract



FIG 2 Gangrene of tip of second left toe at the time of discharge from hospital. Two months before, all toes of both feet were black and appeared gangrenous.

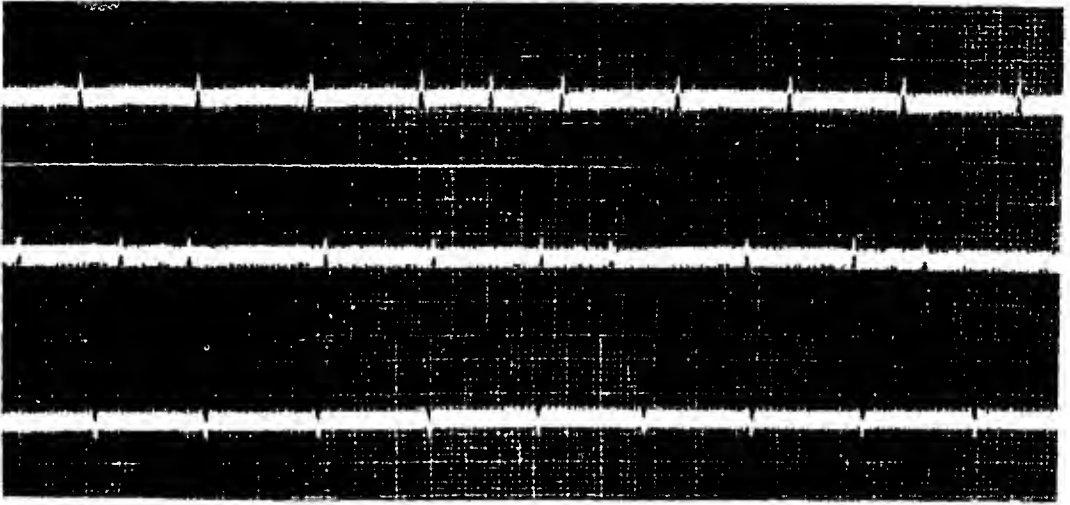


FIG 3 Electrocardiogram, Nov 28, 1930 Normal sinus rhythm Rate 94 Q R S = 0.06 second T flat in all leads Left ventricular predominance Auricular premature beats in leads I and II Low amplitude (maximum 2.5 mm)

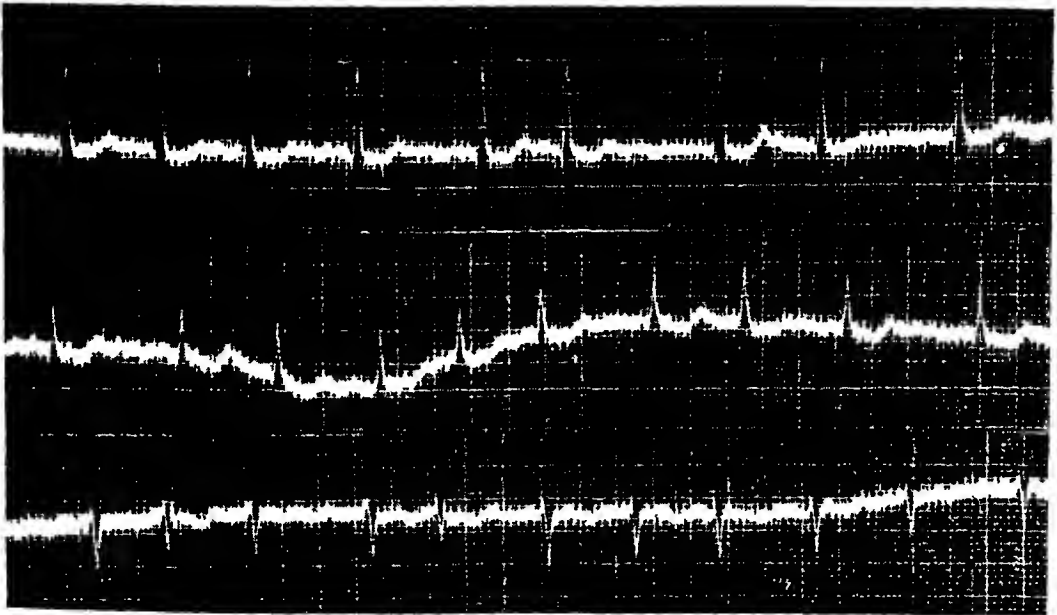


FIG 4 Electrocardiogram, Dec 30, 1930 Auricular fibrillation—rate approximately 115 Q R S = 0.08 second T diphase in all leads Left ventricular predominance

with beginning gangrene of all the digits of right hand, and "splinter hemorrhages" under all the finger nails of left hand. On the 25th there were discolorations of both feet and it is noted that the dorsalis pedis pulsation was felt on the right foot but not on the left, with no impulse at external or internal malleoli of either foot and no popliteal pulsation in either leg. At this time there was a purple area on the right forearm. One day later, two pustules appeared on the right cheek and these developed in 24 hours into an abscess of the upper lip and right side of the face, which was opened. By this time the lungs were clear. All toes of both feet were black all over and apparently gangrenous. By Dec 1st, there was a sharp line of demarcation across metacarpophalangeal joints of all fingers of the right hand.

On Nov 28th, the first electrocardiogram showed a normal sinus rhythm, with auricular premature beats. On Dec 21st, the patient started again to fibrillate. Digitalis, which had been stopped for about a month, was resumed and the heart action became regular for a few days. An electrocardiogram on the 30th showed fibrillation, as also on Jan 3rd, 1931, and although on Jan 5th there was normal sinus rhythm, this did not

continue. Accordingly, after careful trial, the patient was put on quinidine on Jan 7th, and all electrocardiograms taken later, on Jan 15th and Feb 3rd, showed normal rhythm. There was no clinical evidence of fibrillation after January 8th.

At the time of leaving the hospital, the condition of the nose and cheek had completely cleared up, all of the toes had healed with the exception of the terminal joint of the second left toe, while circulation had returned in a considerable part of the fingers and thumb of the right hand.

When discharged on March 1st, 1931, the patient felt better than she had for three years or more.

SUMMARY

1 The case is reported of a patient in whom multiple arterial occlusions occurred coincident with the disappearance of auricular fibrillation.

2 It is believed that the return to normal auricular rhythm was related to the use of pituitrin.

3 It is believed that pituitrin should be used cautiously in the treatment of patients with auricular fibrillation.

REFERENCES

- ¹MACKENZIE, SIR JAMES. Diseases of the heart, 1914, H. Frowde, London, 379, 235.
- ²HARE, H. A. A therapeutic referendum, 1928, *Prog Med*, iv, 311-417.
- ³MEYERS, S. G. Emptying of the gall bladder with especial reference to the use of pituitrin, *Am Jr Med Sci*, 1928, clxxv, 405-410.
- ⁴SCHONDUBE, W. Röntgenologische Beiträge zum Entleerungsmechanismus der Gallenblase, *Fortschr a d Geb d Röntgenstrahlen*, 1927, xxxvi, 603-609.
- ⁵DALE, H. H. The action of extracts of the pituitary body, *Biochem Jr*, 1909, iv, 427-446.
- ⁶WIGGERS, C. J. The physiology of the pituitary gland and the actions of its extracts, *Am Jr Med Sci*, 1911, cxli, 502-515.
- ⁷ROSS, J. B., DREYER, N. B., and STEHLE, R. L. Cardiac action of pituitary extract, *Jr Pharm and Exper Therap*, 1930, xxxviii, 451-460.
- ⁸KOLLS, A. C., and GELLING, E. M. K. Pharmacology of extracts of posterior lobe of pituitary gland, *Jr Pharm and Exper Therap*, 1924, xxiv, 67-81.
- ⁹GELLING, E. M. K., and RESNIK, W. H. Action of pituitary tartrate on heart of unanesthetized dog, *Jr Clin Invest*, 1925, i, 239-245.
- ¹⁰HALSEY, J. T. Organotherapy and hormotherapy, *Endocrinology and Metabolism* (Barker, L. F.), 1922, i, Sec 1, D. Appleton and Company, New York, 114-115.
- ¹¹GELLING, E. M. K., and RESNIK, W. H. Action of pituitary extract on the heart of unanesthetized dog, *Jr Clin Invest*, 1925, i, 217-238.

Hereditary Deforming Chondrodysplasia*

By M A SPANGELBERGER, M D , F A C P , *Denver, Colo*

HEREDITARY deforming chondrodysplasia is a comparatively uncommon disease of the skeletal system, characterized by bony deformities caused by multiple cartilaginous exostoses and enchondromata (bone cysts) Ehrenfried¹, in 1915, collected over 600 cases from the entire medical literature of the world; Stocks², in 1925, brought this number up to 765 Ray³, in 1930, found 156 cases reported in the American literature and added one of his own Since then Hyndman⁴ has published an interesting case report The most recently reported case is one by Blount⁵ in which a mild rachitis was coincident This case, with our own, brings the total number of American cases to 160

Heredity was noted in 83 per cent of the cases reviewed by Ehrenfried, in 75 per cent by Ray and in similar percentages by other authors, however, there remains the minority percentage in which a history of heredity cannot be demonstrated The fundamental etiological factors are still undetermined No satisfactory treatment has been discovered

The exact status of this disorder can be determined only by a larger series of authentic cases and the following case is herewith reported

HISTORY OF PATIENT

Walter W, age 11, of German descent and a native of Missouri, was the first born of three children For six months he was breast fed, then the mother, becoming aware of existing pregnancy, weaned him Several cow's milk formulae were tried Thereafter a diet of strained vegetables, grain gruels, and the lighter cereals was given The child began to creep at nine months, and walked before the end of the year Development proceeded without untoward incident until three and one-half years of age At this time knoblike excrescences were noted in close relation to the joints of the extremities These appeared simultaneously, showing most prominently about the knee joints Locomotion became difficult, and normal movements of the wrist and elbow became limited

A pediatricist was consulted who made a diagnosis of rickets and prescribed a diet rich in calcium Cod liver oil was also given, but no improvement followed Since walking was impossible, a brace was applied, consisting of a belt with metal braces extending along each side of the legs, fastened to soles of specially made shoes This, too, was unsatisfactory and the child continued resting part of the time in bed and part of the time making his way around with unsteady gait and crawling when balance was lost At the age of five, improvement ensued The ability to walk returned weight increased, and the child entered school at six Since that time he has been active, taking part in play as a normal child While he has sustained many falls, there has never been a fracture

The boy came under observation again, not for the disorder herein described but as the result of a survey of all grade

*Submitted for publication, July 13, 1931

school children for faulty breathing. His parents were advised that he required a tonsillectomy. The only other illnesses were pertussis, measles, and mumps at the respective ages of four, six, and eight years. Recovery in each was complete and uneventful.

At the time of the tonsillectomy, a bony spur from the outer condyle of the femur was excised, and a cyst on the anterior aspect of the tibia was curetted.

Father's History The father was 37 years old, white, of German descent, a native of Missouri, and the eldest of nine children. He was reared on a farm and followed agricultural pursuits until 29 years of age. His height was 6 ft. 4 in, weight 224 lbs, of powerful physique. He had never had severe illness or injury. Minute examination of the skeletal system showed not the slightest disorder. The usual laboratory tests, including Wassermann, were negative.

Mother's History The mother was the second of five children, age 35 years, a native of Missouri, and of German descent. She married at 19 and gave birth to this child one year later. Two other children were born 11 months and three years later. She was reared in the country and had the usual childhood diseases with uneventful recoveries. Her health was excellent until five years preceding examination when pulmonary tuberculosis developed. A change of residence was advised, and the family then came to Colorado. Her disease became quiescent and was arrested at the end of two years. At that time she had regained her normal weight of 130 pounds and was apparently in a fair state of health, when a Graves' syndrome began with a rather sudden onset. Thyroidectomy was done and after several months apparent recovery was established. Physical examination now shows a cavitation in the upper right lung, but no signs of activity. Basal metabolic rate is minus two. Usual laboratory tests including Wassermann, negative. As in the instance of the father, a careful examination of the osseous system disclosed no abnormality.

Correspondence with relatives of both parents fails to elicit evidence of any gross

abnormality such as exostoses. Nor is there any report as to unusually short stature or limitation of joint movements.

Physical Examination of Child The patient is a fairly well nourished boy, height 48 inches, weight, 68 pounds. As he stands nude (figures 1 and 2) misshapen joints are strikingly apparent. Knoblike protuberances, of varying size occur at the elbows, wrists, knees, ankles and about the chest and pelvis. These are larger about the joints of the left side of the body. *Manu valgum* and *genu valgum* exist, and these, too, are more marked on the left side. There is a varying amount of limitation of movements in all major joints, he is unable to flex the left thigh on body, pronation and supination of the left hand cannot be fully accomplished. The gait is awkward, but the patient is remarkably agile, despite the disadvantage of distorted joints.

Head The head is symmetrical, the face proportionate, and no exostoses are evident. The hair is fine and abundant, with clean scalp. The skin is warm, smooth, of excellent texture and color.

Eyes Blue, pupils round, equal, react to light and accommodation. A diopter of myopia is measured in each eye. There exists no muscular imbalance. The fundi are normal.

Ears Normal.

Teeth Of good structure, well spaced, and dentition has progressed normally for age.

Throat The tonsils are hypertrophic, exhibiting crypts containing caseous material. A pad of adenoid tissue is visible in the posterior-pharynx.

Thorax The thorax is flattened, but respiration is adequate and equal. There are no adventitious sounds on auscultation of the lungs.

Heart Normal outline of the heart is found on percussion. The apex is in the fifth interspace, one-half inch within the nipple line. The heart tones are normal. There is a brief presystolic murmur at the apex.

Abdomen The abdomen is flat, soft, and no organs or masses are palpated.

Nervous system All superficial and deep reflexes react normally.



FIG 1



FIG 2

FIGS 1 and 2 Anterior and posterior views of patient to show skeletal deformities

Skeletal System The findings are based upon physical examination and a complete x-ray examination of the entire skeleton

Skull There are no exostoses, enchondromata or deformities in the bones of the skull and face

Spine The spine is straight Nearly all the transverse processes are involved

Ribs There is an exostosis on the left fifth rib, near the spine, with some pressure deformity of the fourth rib above this exostosis A larger growth can be felt and seen on the seventh rib in the right mid-axillary line There are also several smaller deformities on the anterior ends of several ribs

Pectoral Girdle There are several exostoses along the superior margin of the scapulae and the glenoid fossa is involved The acromial end of each clavicle is broadened and irregular

Pelvic Girdle There are several exostoses on each ilium The acetabulum on both sides is broadened and shallow The texture of the pelvic bones is coarser than normal

Upper Extremities The humerus on both sides is broadened at the upper end and the shaft of the bone is bowed outward The bones of the forearm on both sides are shortened and bowed, the ends broadened and distorted and there are large exostoses at the lower ends These deformities are most marked on the left side and have resulted in dislocation of the upper end of the radius Carpals, metacarpals and phalanges show abnormal variations in shape and size Several exostoses and enchondromata are noted (Figure 3)

Lower Extremities The neck of each femur is markedly straightened and broadened The trochanters are widened and thickened The texture of the upper end of the shaft is abnormally coarse The lower ends are broad and thick, the contour is irregular and there are several clubbed stalactite growths pointing away from the epiphyses The upper end of each tibia shows the same characteristic stalactite exostoses as described for the femur The upper end of the fibula is broadened and thickened, almost twice normal size, irregular in contour and a large irregular osteoid for-

mation is noted on the posterior surface (Figure 4) The lower end of the diaphysis of the left fibula is expanded to three times normal diameter by a large enchondroma, a similar deformity, not quite so marked, is noted on the lower end of the right tibia The bones of the feet show about the same degree of pathological change as the bones of the hands

Laboratory Examinations Hemoglobin, Dare, 92 per cent, red cells, 4,100,000, white cells, 5600, Wassermann test negative Several estimations of blood calcium gave values within normal limits Urine acid, sp gr, 1.020, sugar, bile, acetone, and indican tests were negative No pus cells, red cells or casts were seen, and crystalline deposits were normal The test for Bence-Jones' protein was negative

DISCUSSION

Since the various features of this disorder have been thoroughly discussed in many papers we shall consider only those which have a direct bearing on this case

The physical findings establish the diagnosis The short stature, the shortening of the extremities with deformities at the elbows, knees, wrists, and ankles, the inability to extend the forearms fully, the multiple palpable and, in part, visible exostoses near the ends of the long bones are characteristic The roentgenograms show many enchondromata and many spurs, arising chiefly from the metaphyses near the epiphyseal junctions The x-ray pictures of the enchondromata have the soap bubble appearance of a benign giant cell tumor In giant cell tumor exostoses do not develop, the disease is progressive, accompanied by much pain, and eventually results in fracture, extension by spontaneous perforation or surgical interference Simple, non-hereditary

osteomata, chondromata and enchondromata are usually single. According to Honeij⁶ the bones in chondrodysplasia are very sensitive to trauma and easily respond by formation of exostoses. Osteitis fibrosis cystica does not produce the exostoses and the curettings of a cyst determine the diagnosis.

The case under discussion was diagnosed by several consultants as rickets. This diagnosis seems plausible in view of the history of feeding by the mother until she was five months pregnant. Roentgenograms at

this time might possibly have determined the correct diagnosis.

Hyndman⁴ gives a very satisfactory differential diagnosis between chondrodysplasia and chondrodystrophia fetalis. He rightly points out that the latter is a generalized disease usually involving all the epiphyses equally and producing a symmetrically dwarfing skeletal deformity which is usually well developed at birth and therefore dates back to intrauterine life.

Although true heredity and familial incidence in this disease has been unquestionably demonstrated by many



FIG 3 X-ray of forearms. Note shortening and bowing, and exostoses and enchondromata.



FIG 4 X-ray of knee joints Note enchondromata and stalactite exostoses

authors, a careful search into the family history of the patient revealed no other cases. However, a hereditary history is often lacking, as in this case. Possibly the stigmata of this disease may at times be so insignificant that they would be overlooked except on the most careful physical examination, including a complete x-ray examination of the skeletal system. It may also be that those cases in which actually no hereditary basis exists can not be considered as true examples of this disease, even though the physical findings are typical. Ehrenfried¹ coined the name "hereditary deforming chondrodysplasia", other authors have used other names because they did not

agree with his conception of the major features. It may finally be that the hereditary factor is not found in some disturbance of the bone anlage, but in some disturbance of the endocrine system. In that case the changes in the skeleton may appear only in certain cases of such endocrine disturbance. In our case there is a history of very severe exophthalmic goiter during the pregnancy of the mother. Jegat⁷ suggests that tuberculosis may have an etiological significance. Although there is a history in this case of tuberculosis in the mother, the evidence for such a conclusion is unconvincing. The importance of heredity in this disease has been established be-



FIG 5 Cross section of exostosis from left femur Note disorderly growth of cartilage and bone

yond all reasonable doubt But is it not possible that the hereditary factor is to be found in an underlying disturbance of the endocrine system?

Whatever the real cause may be it results in a chaotic growth of the metaphyseal-epiphyseal line The deformities resulting may in part be due, as Keith⁸ has suggested, to a failure of proper pruning of the ends of the long bones and for this reason he calls this disease "diaphysial aclasis"

Microscopically, the picture presented is one of disorderly cartilaginous growth with irregular ossification as shown in figure 5, a cross section of an exostosis, and in figure 6, curettings from an enchondroma in the lower end of the femur These sections correspond to the pathologic changes so beautifully described by Ehrenfried¹ and Honeij⁶

Symptomatology in this disease depends upon interference by the deformity with motion, blood and nerve supply, upon secondary changes such as inflammation and upon true tumor formation Hyndman⁴ believes that all cases of hereditary deforming chondrodysplasia should be carefully checked from time to time to detect immediately any possible true neoplastic changes If such occur he advises prompt and complete surgical excision

Sulphur, phosphorus, calcium, and magnesium determinations in the blood and the urine have so far not given any clew as to rational treatment in this disease Certainly calcium therapy does not produce the beneficial effects that it does in rickets If the disease is a true hereditary disease determined in the bony anlage perhaps no satis-

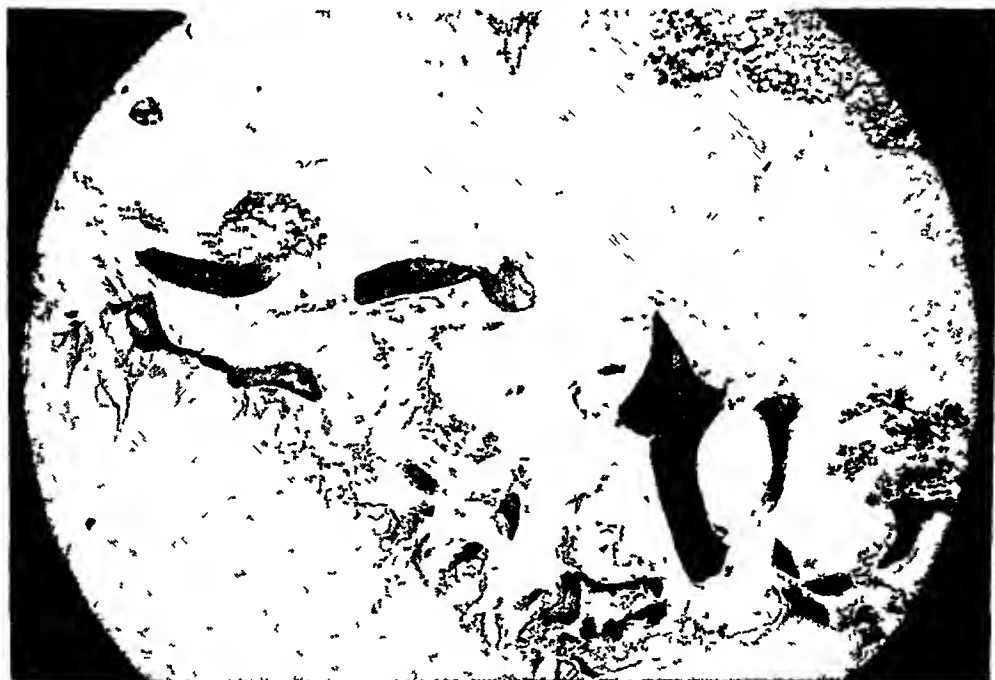


FIG 6 Curetting from enchondroma of left tibia Note atypical cartilage and abnormal bony growth

factory treatment will ever be discovered

SUMMARY

A case of hereditary deforming chondrodysplasia is reported.

No evidence of hereditary origin could be discovered

There was a history of exophthalmic goiter and of tuberculosis in the mother

REFERENCES

- ¹EHRENFRIED, A Multiple cartilaginous exostoses—hereditary deforming chondrodysplasia A brief report on a little known disease, Jr Am Med Assoc, 1915, lxiv, 1642-1646
- EHRENFRIED, A Hereditary deforming chondrodysplasia Multiple cartilaginous exostoses A review of the American literature and a report of twelve cases, Jr Am Med Assoc, 1917, lxviii, 562-568
- EHRENFRIED, A Hereditary deforming chondrodysplasia More cases Am Jr Orthop Sug, 1917, xv, 463-478
- ²STOCKS, P Hereditary disorder of bone development In The treasury of human inheritance, 1925, 3, Cambridge University Press, New York
- ³RAY, H H Diaphysial aclasis hereditary deforming achondrodysplasia Arch Ped, 1930, xlvii, 152-164
- ⁴HYNDMAN, OLAN R Hereditary deforming chondrodysplasia Report of a case Arch Surg, 1930, xxi, 12-31
- ⁵BLOUNT, W P Chondrodysplasia An unusual case Am Jr Dis Child, 1930, xl, 327-333
- ⁶HONEIJ, JAMES A A study of multiple cartilaginous exostoses Four cases with report of calcium and magnesium metabolism in two cases Arch Int Med, 1920, xxv, 584-627
- ⁷LENOBLE, M E, and JEGAT, M Y Trois cas d' exostoses ostéogéniques héréditaires et familiales Bull et mém Soc méd d hôp de Par, 1922, xlv, 1661-1669
- ⁸KEITH, A The true nature of the condition known as multiple exostoses, Tr Med Soc Lond, 1920, xlii, 67-74

The Dietetic Control of Some Forms of Hypertension and the Associated Gastrointestinal and Nervous Symptoms*

By V C ROWLAND, M D , F A C P , *Cleveland, Ohio*

IT IS extraordinary, in view of the available facts, that the profession has so largely ignored the therapeutic possibilities of diet and weight control in certain forms of hypertension associated with plethora and gastrointestinal and nervous symptoms

By way of introduction, a brief reference to the literature of hypertension will be of interest

From the time of George Johnson in 1868, and of Gull and Sutton in 1872, the subject of vascular disease has been continuously studied, and approached mainly from the pathological viewpoint. After much controversy as to the characteristic changes in the intima and media, there seems to be fairly general agreement with the views of Fischer and Schlayer in 1910, and of Brogsitter in 1924, and of Kernohan, Murphy and Grill in 1930, namely, that the primary change is an hypermyotrophy of the media or at least a thickening of the arterial muscle wall with an increased number of nuclei which may be interpreted as a hypertonic contraction in response to some hypothetic pressor substance, or

some stimulus to the sympathetic nerves. The thickening of the muscular layer of the vessels is not necessarily associated with any primary degenerative change. Later there may be proliferation of the intima and subsequent hyaline or other degeneration. Kernohan, Anderson, and Keith, in 1930, reported an extensive study of hypertension from biopsies from muscular tissue showing a similar thickening of the muscular layer. Ophthalmoscopic evidence, such as that of Volhard in 1931, also seems to confirm the idea of a primary contraction and only subsequent degenerative change.

There have also been a few disconcerting cases of essential hypertension with death by cerebral or other accident, with absolutely negative pathological findings. These cases, together with much clinical evidence, suggest the conception of Clifford Allbutt, that there is a functional stage of hypertension, and that the characteristic pathology of diffuse vascular disease is the result rather than the cause, contrary to current pathological opinion. Furthermore, it is generally agreed that there is no sharp classification of the different forms of hypertension that they differ mainly in degree, that

*Given before the American Gastro-Enterological Association at Atlantic City, May 4, 1931

either benign or malignant hypertension may run a progressive course with very moderate elevation of blood pressure, and that much advanced vascular sclerosis may have no elevation of blood pressure whatever

The literature of obesity also is important as a background to the following report upon the dietetic management of some forms of hypertension. Insurance statistics, largely ignored by the medical profession, have for years repeatedly confirmed the association of increased blood pressure and high mortality rates with obesity. The Actuarial Society of America, in 1925, published a compilation of the results of the statistics of twenty-six companies, and a similar forthcoming compilation of a larger and better controlled set of statistics, it is said, will confirm, that approximately two-thirds of all individuals over forty years of age, who are ten pounds or more overweight, show a definite elevation of blood pressure. Similar figures were shown in private studies of obesity, such as that of a thousand cases in Boston by Preble in 1923. There is some statistical evidence, also largely ignored, of the lowering of blood pressure by reduction in weight.

Furthermore, the literature of the more scientific type on the subject tends to the idea that obesity is largely exogenous (Newburgh). Students agree, as Bauman states, that there is no inherent change in the basal metabolic rate, except in the subthyroid group. The work of Grafe and others points to a compensatory rise in the basal metabolism during periods of overfeeding. Increased metabolism implies increased blood pressure and

pulse rate. There is, of course, a type of obesity with low blood pressure and low metabolism. However, as Evans has recently shown, if basal metabolism rates are calculated on normal rates for the height and age of obese individuals, instead of actual weights, many of these rates will be high instead of low, and thyroid medication clinically unsatisfactory, as might be expected. There is evidence pointing to a lower specific dynamic action to protein in certain obese individuals. This is not constant, however, and can only be one factor in the obesity, possibly due to deficiency of anterior pituitary function (Liebesing).

The type of patient who presents the form of blood pressure most amenable to dietetic control is one in his forties or early fifties, definitely overweight, ruddy, strong, and active, eating heartily of rich food, not too fond of muscular exercise, and not too highly nervous. He is usually seen in private practice in the so-called higher social levels, although in our country and generation, even in hard times, high caloric food, if not wholesome balanced diet, is freely available and obesity abounds well down the social scale. The patient is either symptom free or beginning to show minor nervous and digestive symptoms such as palpitation, headache, heartburn, and flatulent indigestion. Frequently he has gained twenty or thirty or more pounds over his optimum weight at twenty-five or thirty years of age. He may complain of lack of initiative or slight lack of endurance in comparison with his earlier working capacity. If his blood pressure had been observed, there was considerable fluctuation with

a general tendency toward a higher and more continuous blood pressure level. Frequently, but not invariably, there is a family history of the apoplectic habitus and high blood pressure or of obesity and diabetes. The most suitable cases show no organic pathology or very early signs of cardiac enlargement and aortic fullness fluoroscopically. Presumably, the hypertension is due to a functional arterial hypertonus or that with an early and often controllable stage of diffuse vascular disease. Our ideal patient is intermediate between the young individual with very high systolic and diastolic pressure and the older patient with advanced arteriosclerosis or marked kidney pathology.

As indicated below, a reducing regimen in this group of cases effects a very prompt reduction in blood pressure and by maintaining weight at or near a normal level, permits of sustained control of the blood pressure to a degree not generally appreciated. There is, apparently, also a functional moiety in the hypertension associated with advanced cardiovascular disease which may be gradually reduced to the optimum level as determined by the increased peripheral resistance. For purposes of practical therapy, therefore, the most useful classification, if not the clearest in the present confusion of the subject, is that of functional hypertonus and fixed hypertension of organic peripheral obstruction.

With this introduction, we may approach the following observations upon the relationship between diet, weight, hypertension, and associated symptoms.

From personally kept records of

private patients over a period of years, one hundred cases were selected for this study. All blood pressure observations were made personally by the writer under the same conditions. In the tabulation, part of which appears below, the first weight given is the weight of the patient at the beginning of management, the second is the patient's statement of weight in early adult life in health, usually about twenty-five years of age, as a guide to normal weight, the third is the weight at the end of a period of management, mainly by diet. This was a balanced diet of milk, egg, meat, vegetable, and fruit, simply low in sweets, fats, pure starches and total calories. Huchard's idea that the quality of food stuffs is more important than the quantity has never been supported. However, excess of protein was avoided in our diets. Salt restriction played no part, although seasoning, condiments and stimulants were interdicted during the period of management. Frequently a prompt drop of five or ten pounds is noted the first week. Later, however, one pound a week was the goal. In all cases, reduction was kept at a rate which gave an improved sense of well being, not weakness or distress. The beginner was often hungry with the sudden change in his habits of eating. In fact gastric analysis in a few cases showed hypersecretion and hyperacidity in comparison with readings taken after there had been time for adjustment to the reduced diet. Clinically too, after this adjustment, many patients testified that they no longer had the craving for excessive food intake. A minimum of medication was used, usually a little bromide or luminal for

short periods for symptomatic relief. Thyroid extract likewise was used only occasionally and in small dosage. No nitrites, sulphocyanates, calcium, atropine, bismuth salts, or other drugs were used in the reported cases. None of the cases recorded were taken off their usual schedule of work. Associated conditions were noted such as indigestion, ulcer, gall bladder disease, dia-

betes, thyroid disorders, menopause, cardiovascular disease, nervous disturbances, urticaria and other eruptions, focal infection, arthritis, etc.

A sample of the method of tabulation of data follows together with individual and composite graphs of weight, systolic and diastolic pressure, and, in diabetes, of blood sugar.

TABLE I

No	Sex	Age	Weight	Blood Pressure	Associated Disorders	Urine	Blood Sugar	Period of Treatment
9	F	70	190	210/110	old hemiplegia	neg	140	2/27/30
			150		arthritis			
			161	130/80				4/24/31
19	F	65	172	190/95	much pyrosis	alb	180	2/10/23
			120			ft		
			135	130/80			109	3/19/28
25	F	70	151	230/90	sour eructations		153	8/7/29
			95		nausea			
			135	140/70			95	1/23/31
28	F	51	200	200/95	exhaustion	sugar	240	10/12/28
			125		edema of feet	cystitis		
			166	130/80				11/13/30
34	F	60	179	215/110	vertigo	casts	88	10/26/28
			135		familial	alb		
			151	140/80	hypertension			12/15/28
41	F	58	138	170/90	neuralgias	sugar	108	7/10/30
			115			once		
			123	120/75				4/20/31
50	F	49	160	215/110	pyrosis	neg		2/8/30
			125		dent inf			
			140	115/80	palpitation			8/8/30
56	M	62	190	220/140	cardiac	alb		1/24/27
			150		enlargement	casts		
			158	160/90	gall stones			12/31/30
60	F	68	180	170/85	diabetes		106	2/3/31
			130					
			151	140/68				3/20/31
64	F	50	151	150/90	indigestion	alb	101	10/12/29
			123		urticaria	ft		
			127	130/80				2/28/30
67	F	68	143	250/90	indigestion	neg		2/11/29
			98		flatulence			
			124	170/75				7/15/29
68	F	50	144	170/100	gout	neg	100	12/4/28
			120		Wassermann++++			
			132	130/87				3/12/29
73	M	42	202	160/80	chronic	neg		12/17/30
			185		indigestion			
			177	120/80				1/28/31
79	F	50	190	210/100	indigestion			3/24/24
					"rheumatism"			
			157	120/80				4/24/31
100	F	59	168	220/110	hereditary			4/13/27
			125		hypertension			
			164	135/78	angina pectoris			4/25/31

From the family histories, it is very apparent that heredity plays a definite rôle in the individual tendency to hypertension and also to obesity, but instead of accepting this as inexorable, efforts at prevention are shown to be very definitely worth while. As in

diabetes, also with an hereditary predisposition, the latent tendency need not always become manifest. On the contrary, when carbohydrate metabolism is impaired full control allows improved function. Ten cases of diabetes are listed among the hyperten-

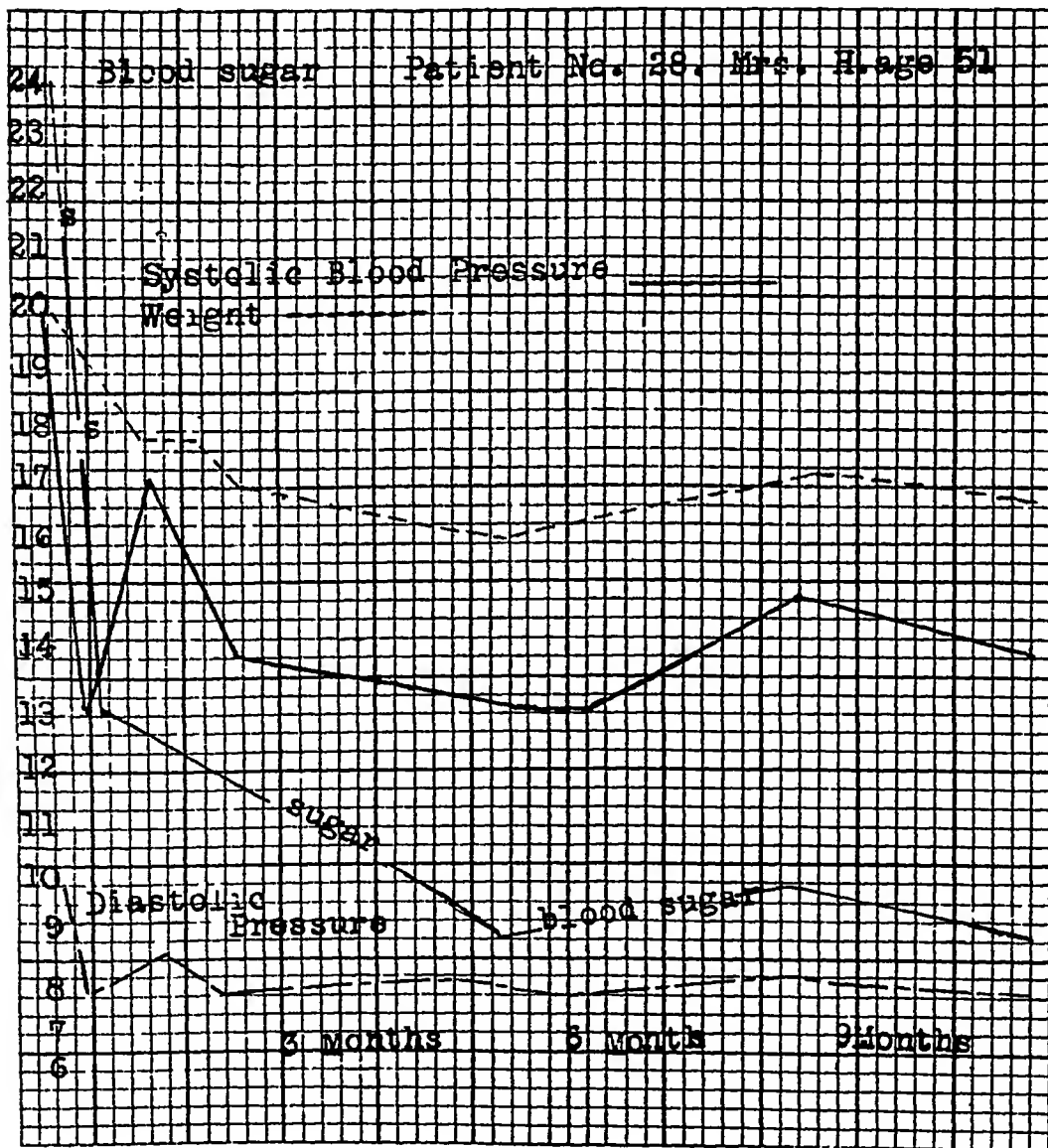


CHART 1, Patient 28. A woman of 51 years with an initial weight of 200 lbs, blood pressure 200/98, blood sugar reading of 240 mg, and sugar in the urine. Under dietetic management and observation for one year, final readings were weight, 166, blood pressure, 138/80, blood sugar, 90. Relief from weakness, dyspnea and palpitation.

sion cases and the hypertension curve nearly parallels the hyperglycemic curve

Typical cases of weight reduction with prompt response in blood pressure are shown graphically. The range in total weight reduction was 0 pounds to 54 pounds and in systolic blood pressure from 10 mm of mercury to 105 mm. The average weight loss for the 100 cases was 20.06 pounds. The average drop in systolic pressure was 40.85 mm, in diastolic pressure, 17.32 mm. The average period of management was 8.28 months.

Many of these cases were seen at long intervals for years afterwards with blood pressures controlled in proportion to their weight control. Preliminary to this report (April, 1930) a group was rechecked. The following is an example.

Case 10, a woman seen in 1924, with a blood pressure of 210/110 and weight of 190, now shows a pressure of 120/80 and weight of 157, at 57 years of age. She has entirely and very intelligently changed her habits of eating, has lost all craving for rich desserts and heavy eating, but has continued at her same occupation during the whole period of seven years.

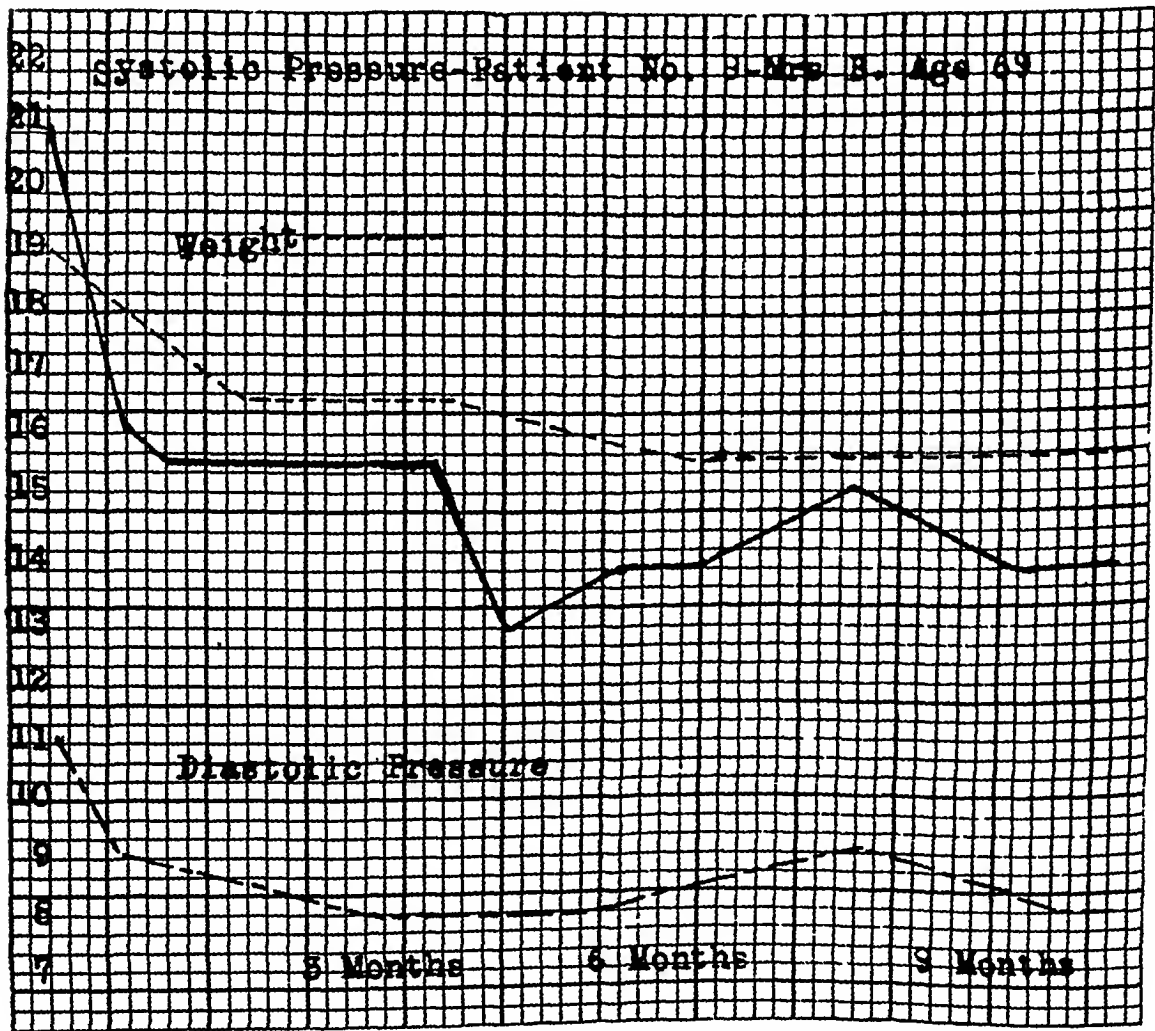


CHART 2, Patient 9. A woman of 69 with initial weight, 190, blood pressure, 210/110. First year of management reduced weight to 155 and blood pressure to 140/82. Relief from severe neuralgias and "rheumatism."

It is recognized that some error occurs in certain cases in that the first readings may be high on account of nervousness and acute upsets which suggest their seeking medical advice at the time. At best there are fluctuations which must be averaged over a period of time. With care, however, this error can be fairly well discounted and with observation over a long pe-

riod, the reaction of a given patient to strain, to the menopause, and to acute infections can be noted and the blood pressure compared with the original reading. In the cases reported, no factor was as important as that of weight. After full adjustment at the reduced weight levels, the blood pressure was much more constant even under extra strain.

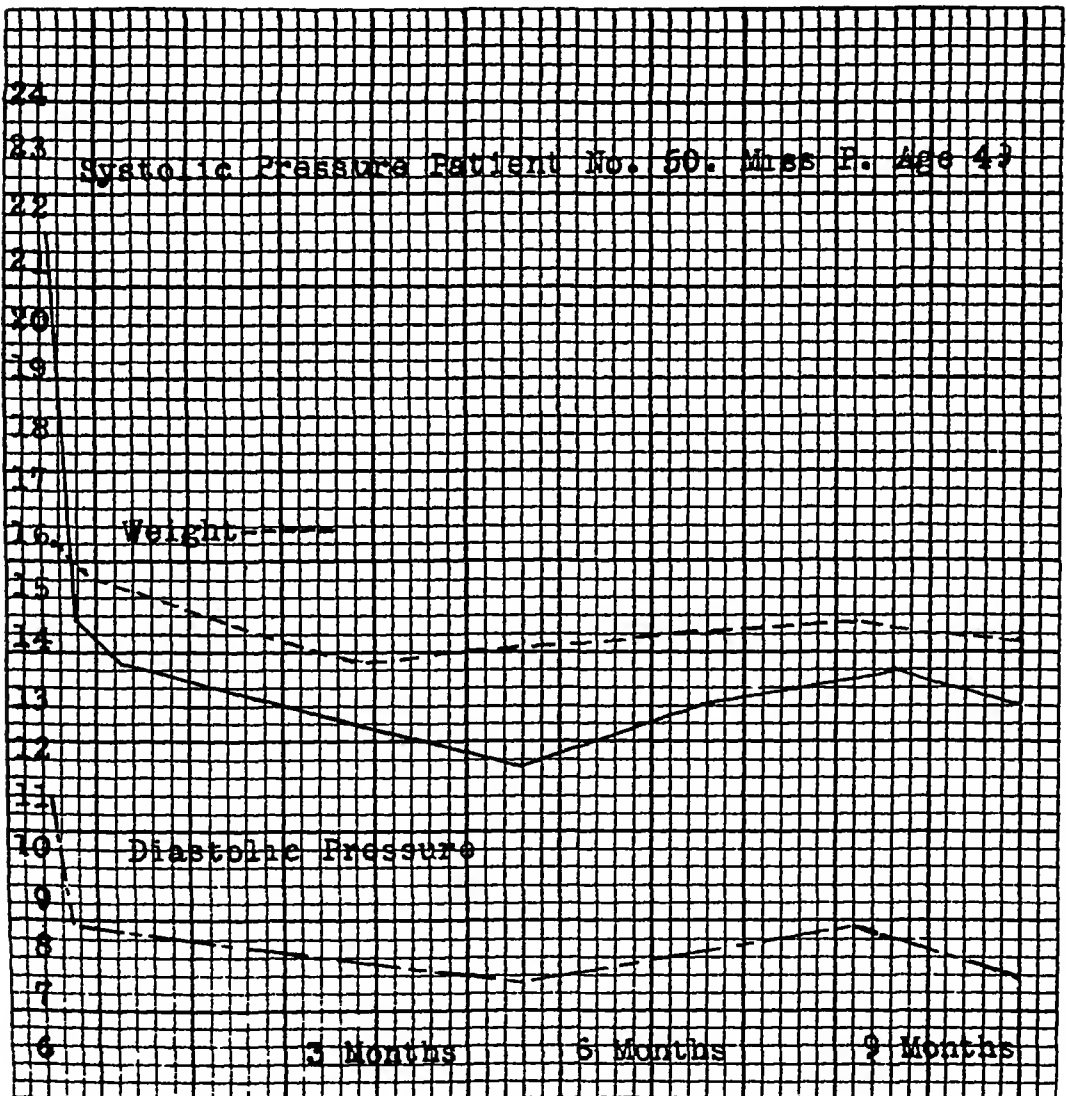


CHART 3, Patient 50. A woman of 49 with initial weight 160, blood pressure, 215/110. First year of management reduced weight to 140 and blood pressure to 130/78. Relief from weakness and indigestion.

Case 41, for example, is a teacher of 58, seen first in vacation time, July, 1930, symptom free at the time although she had had much neuralgic pain. She did not appear to be much overweight at 138 pounds but she was eating heartily and her early adult weight was 115 pounds. Under management she very gradually reduced to 123 with blood pressure reduction of 170/90 to 125/75 which remained quite constant during the following teaching year, the last observation being on April 18, 1931.

Relapses with marked increase in weight as in case 56 (shown in the graphic record) show the direct effect of increased weight on blood pressure after a prolonged pe-

riod of control. Relapses are not so common as might be expected, especially among intelligent people under intelligent and conscientious supervision and with proper regard for normal balance and variety in diet.

ASSOCIATED SYMPTOMS

Nervous and digestive symptoms most commonly accompany the hypertension. Of the former, headache, neuralgias, paresthesias, vasomotor instability, palpitation, insomnia, nervous irritability to the point of a definite psychosis, all have occurred and

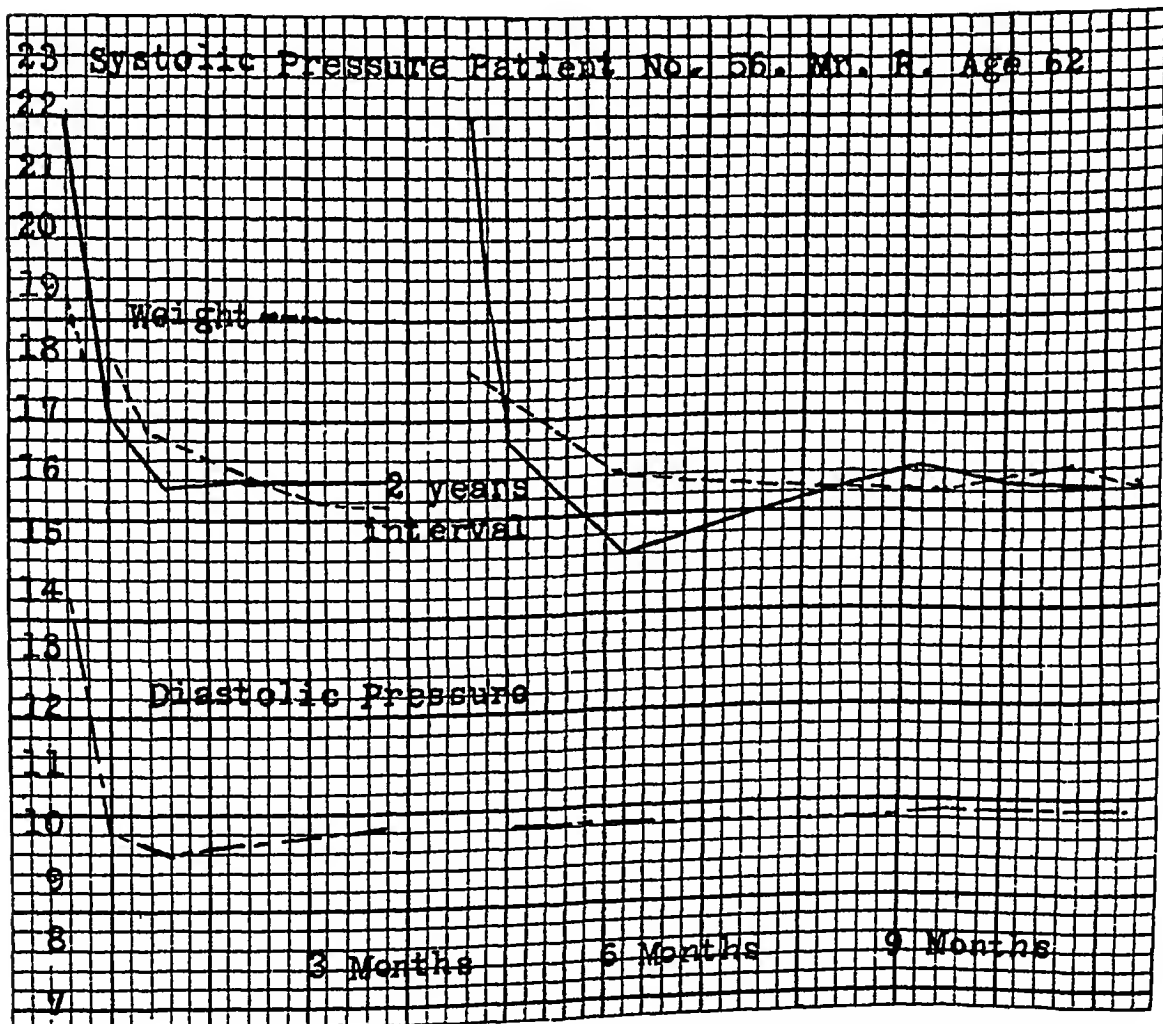


CHART 4, Patient 56. A man of 62, initial weight of 190, blood pressure 220/40. Reduced in 4 months to 155 pounds and blood pressure of 160/100. Relapse for 2 years, gaining weight to 176 with pressure of 220/100. Maintained for 6 months at 160 to 155 pounds with pressure 145 to 160/100.

have been relieved to an extraordinary degree

Digestive symptoms range from simple distress, pyrosis, eructations, flatulence, nausea and vomiting to a frank gallbladder type of dyspepsia or ulcer syndrome. An analysis of the histories showed seven per cent of clinical diagnoses of gall bladder disease, three confirmed by operation, and four similar diagnoses of ulcer, none of which were confirmed by operation. It is quite probable that more cases had had at some time during their history definite peptic ulcer, since the symptoms were often highly suggestive. X-ray studies were not made in cases that responded promptly to dietetic management of the hypertension. This suggests caution and individualization in the treatment of ulcer so that the older ulcer patient with a tendency to weight and hypertension is not eventually hurt more than helped by frequent high fat feedings such as the full Sippy diet.

Furthermore, there occurs as a complication of hypertensive cardiovascular disease a very intractable form of ulcer with deep craters and rapid erosion leading to hemorrhage or perforation. Autopsies often show these lesions associated with advanced circulatory pathology. Sometimes the ulcer seems to be of the nature of a terminal complication. Accordingly, whatever aggravates the hypertension and circulatory strain, such as a high caloric diet, would be a bad form of ulcer treatment.

Healed ulcer cases who gain unduly in weight often show symptoms suggestive of recurrence. That one can make this diagnosis too hastily is shown

by a case in which the writer had an unusual opportunity due to the accidental death of the patient of showing a scaphoid cicatrized fossa in the duodenum with no hint of recent ulceration or inflammation. Deformity of the duodenum had been apparent by x-ray shortly before death, similar to that observed several years before following treatment for typical symptoms and profuse hemorrhage. His recent symptoms were apparently due to heavy eating *per se*. The case is instructive as suggesting that the ulcer syndrome even in a former ulcer patient may precede actual ulceration, and that the latter is but an incident in, or a complication of, a primary metabolic, or other disorder.

Gallbladder disease with its relation to the cholesterol metabolism and its frequent association with the overfed type of patient is even more closely related to hypertension. Likewise very suggestive symptoms may result from the metabolic disorder *per se* without organic disease demonstrable even at autopsy. Many of these symptoms are relieved by the reducing management. In the above 100 cases, there were 26 cases with chronic indigestion of varying degree besides the 7 diagnosed as definite gall stones or gallbladder disease. At least 22 of the 26 were satisfactorily relieved.

The gastroenterologist has a great therapeutic opportunity in the simple dietetic management of these cases. The incidence of hypertension and excessive weight is enormous and apparently increasing in our generation. Janeway found 111 per cent of 7872 cases in private practice with blood pressures above 165. Deaths from

hypertension and its complications in the United States are said to number 140,000 annually. Diet has gotten into disrepute because of the many weird abuses under that name, but will undoubtedly play a larger rôle in health supervision in the future. With the new emphasis on preventive medicine, now arrived at the stage of individual participation, we may expect the matter of diet to be brought more in line with medical science.

SUMMARY

1. The literature of essential hypertension indicates that the primary structural change is an hypermyotrophy of the media of the arterioles and that degenerative changes are secondary. Functional hypertonus occurs, in rare cases without demonstrable

pathology even at autopsy. A hypothetical pressor substance of metabolic or glandular origin is postulated as the causative agent.

2. The literature of obesity shows an unmistakable association with hypertension. Approximately 66 per cent of all people over 40 years of age and 10 pounds or more over weight show hypertension.

Obesity is largely exogenous.

Metabolic rates are usually normal, sometimes increased.

Mortality rates are increased in proportion to the excess in weight.

3. Heredity is a strong predisposing factor in hypertension and obesity as in diabetes and other diseases.

4. A balanced reducing diet intelligently supervised is the largest single

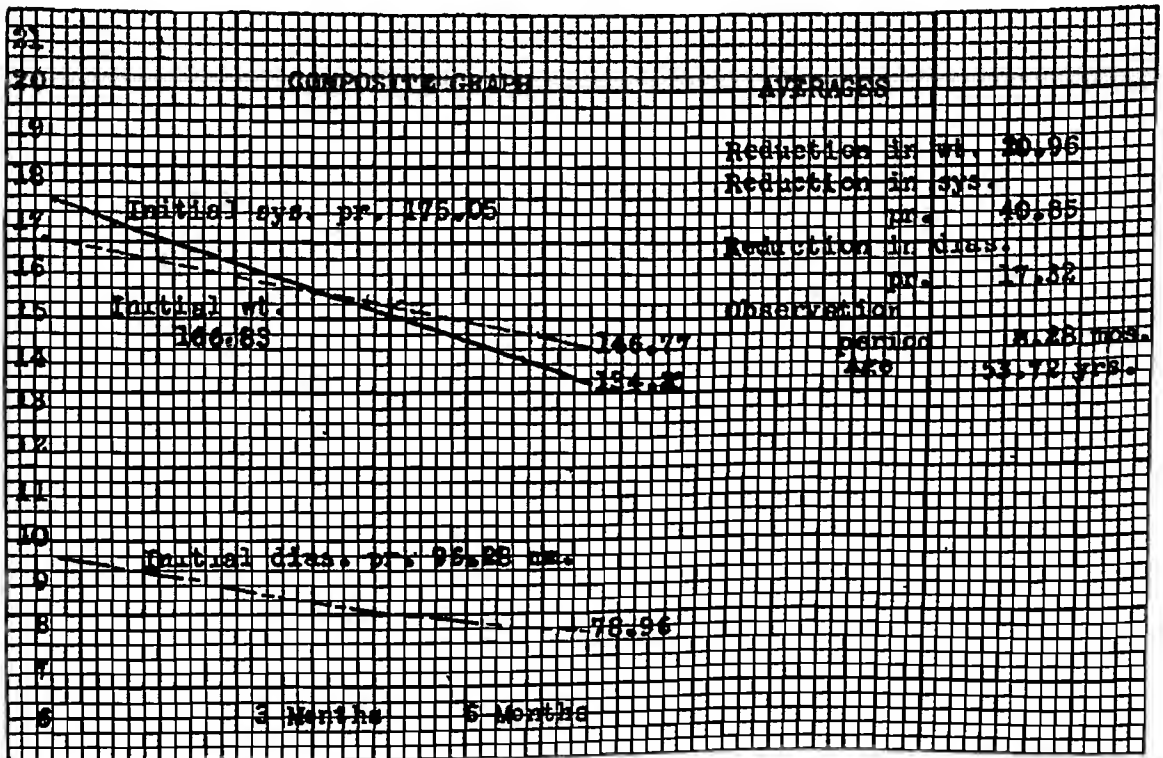


CHART 5 Graph of averages in 100 private patients personally observed at weekly to monthly intervals. Initial weight, 166.83 pounds. Reduced to 134.20 pounds over an average of 8.28 months. Pressure reduced from 175.05/96.28 to 134.20/76.96.

factor in the control of certain types of hypertension and the associated symptoms. It is more efficacious and more practicable than is generally appreciated.

5 One hundred private patients personally observed, many for long periods, showed the following average figures:

Initial weight	166.83 pounds
Initial systolic pressure	175.05 mm Hg
Initial diastolic pressure	96.28 mm Hg
Period of observation	8.28 months
Age	53.7 years

Reduction in weight	20.06 pounds
Reduction in systolic pressure	40.85 mm Hg
Reduction in diastolic pressure	17.32 mm Hg

6 In indigestion, gallbladder disease, and peptic ulcer, after middle life and especially with the tendency to hypertension, high caloric diets should be avoided.

7 Weight control after middle life presents one of the largest opportunities for personal prophylaxis and may be carried out in connection with the periodic health examination.

REFERENCES

- BAUER, J. Über Fettsucht, *Wien klin Wchnschr*, 1926, xxxix, 233-237.
- BAUMAN, L. Obesity: recent reports in the literature and results of treatment, *Jr Am Med Assoc*, 1928, xc, 22-24.
- DUBLIN, L. I., FISK, E. L., and KOPF, E. W. Physical defects as revealed by periodic health examinations, *Am Jr Med Sci*, 1925, clxx, 576-594.
- FISK, E. L. The relationship of high blood pressure to other impairments, *Am Med*, 1923, xxix, 446-454.
- FOSTER, N. B. The relations of hypertension to cardiorenal diseases, *Am Jr Med Sci*, 1922, clxiv, 808-819.
- GRAFE, E. Theorie und Praxis der Entfettungskuren, *Med Klin*, 1929, xxv, 373-375.
- GRAFE, E., and KOCH, R. Über den Einfluss langdauernder, starker Übernahrung auf die Intensität der Verbrennungen im menschlichen Organismus (Untersuchungen bei Mastkuren), *Deutsches Arch f klin Med*, 1912, cvi, 564-591.
- KERNOHAN, J. W., ANDERSON, E. W., and KERR, N. M. The arterioles in cases of hypertension, *Arch Int Med*, 1929, xlv, 395-423.
- KREMER, D. N. Obesity, observations on treatment by dietary measures, *Ann Int Med*, 1930-31, n s iv, 909-917.
- LIEBESNY, P. Die spezifisch-dynamische Eiweisswirkung, *Biochem Ztschr*, 1924, cxliv, 308-350.
- MASTER, A. M., and OPPENHEIMER, E. T. A study of obesity: circulatory, roentgen-ray and electrocardiographic investigations, *Jr Am Med Assoc*, 1929, xcii, 1652-1656.
- NEWBURGH, L. H., and JOHNSTON, M. W. Endogenous obesity, misconception, *Jr Am Dietet Assoc*, 1930, v, 275-285.
- PREBLE, W. E. Obesity: observations on one thousand cases, *Boston Med and Surg Jr*, 1923, clxxxviii, 617-621.
- ROLLY, F. Zum Stoffwechsel bei der Fettsucht, *Deutsche med Wchnschr*, 1921, xlvii, 887-889.
- ROSE, R. H. Weight reduction—its indications in high blood pressure, *Am Med*, 1923, xxix, 418-420.
- TERRY, A. H., JR. Obesity and hypertension, *Jr Am Med Assoc*, 1923, lxxxi, 1283-1284.
- WANG, C. C., STROUSE, S., and SAUNDERS, A. D. Studies on the metabolism of obesity. III. The specific dynamic action of food, *Arch Int Med*, 1924, xxxiv, 573-583.

An Evaluation of Stool Vaccines in Chronic Irritable Colon Therapy*†

By JOHN G MATEER, M D, F A C P, and JAMES I BALTZ, M D,
Detroit, Michigan

THERE are several conceptions regarding the etiology of the condition variously designated as chronic irritable colon, neurogenic mucous colitis, chronic non-ulcerative colitis, or mucous colopathy. Barker¹, Bockus², Jordan³, Lichty⁴, and the writer⁵, have emphasized the importance of neurogenic factors in aggravating irritable colon symptoms, and the need for their control in any adequate program of therapy. Dorst and Morris⁶ have recently emphasized the theory that chronic irritable colon is probably an allergic state, due to absorption of the foreign protein of certain stool bacteria. Others have contended that this condition is essentially a chronic infection, involving the wall of the colon, and that the term colitis can be properly applied, therefore, to this large group of cases.

Satisfactory therapeutic results can be obtained in a number of these cases from the employment of a comprehensive program, including the control of various neurogenic factors, bland diet, physiological regulation of the bowels,

antispasmodics, and in some instances, changing the stool flora with lactodextrin and acidophilous milk. Certain obstinate cases, however, are resistant to the above types of treatment, and present an important therapeutic problem. Because of this fact, mainly, and also in view of the lack of agreement regarding the underlying etiology, it has seemed worthwhile to evaluate the practical effectiveness of vaccine therapy in these cases, and also to study the validity of the allergic theory. An abundance of material has been available, and it has therefore been possible to conduct our work upon a selected group of obstinate, irritable colon cases.

Only those autogenous stool vaccines were used, which produced definite, specific skin reactions with intradermal tests. Obviously this does not mean necessarily that the therapeutic results obtained were specific in character, viz, due to a direct effect of the vaccine upon the underlying etiological factor. *A priori*, the possibility of a non-specific mechanism, with a general, systemic effect, must be recognized.

METHOD AND ITS EVOLUTION

Warm stool specimens were cultured and vaccines prepared which con-

*Read before the American Gastro-Enterological Association, Atlantic City, May 5th, 1931.

†From the Gastro-Intestinal Division of Medical Department, Henry Ford Hospital.

tained originally one and one-half billion organisms per cubic centimeter. The vaccines were prepared according to the method of Hartman⁷ and Jackson. In the more *recent* therapeutic experience with detoxified vaccines, detoxification has been carried out by subjecting viable, rather than heat killed, suspensions of the various strains to a concentration of one per cent purified and tested sodium ricinoleate for fifteen hours. The organisms were washed, then, several times with normal saline, to eliminate the sodium ricinoleate, and its irritating effect. Finally, trikresol (0.4 per cent) was added, as a preservative, and to provide sterilization.

Vaccine skin tests were carried out in *all* cases with *unaltered vaccine*, not subjected to sodium ricinoleate, and 1/20 c.c. of each vaccine was injected intradermally. These injections were made upon the flexor aspect of the forearm in all male patients, and upon the extensor surface of the thigh in female patients. The skin reactions were noted twenty-four hours later, as this seemed to be the optimum interval. The patients showing skin sensitivity were then started on vaccine injections of the one or more organisms to which they had reacted.

As a rule the first therapeutic dose of vaccine consisted of a total dose of one minim, containing the one or more organisms indicated, and injected subcutaneously. Subsequent injections were given at intervals of three to seven days, depending upon the degree of transient reaction of the patient to the last injection. In the earlier experience, the dose was increased about two minims each time.

Since this increase, with a vaccine to which the patient was hypersensitive, led to a certain number of disagreeable reactions, it has been the custom for some months to increase the dosage not more than one minim per injection. Furthermore, if a patient had any appreciable reaction to this increase, the same dose was administered as was given at the previous injection, or a smaller dose. A course of treatments consisted of six to ten injections, with an average number of eight. The maximum dosage, therefore, consisted of eight minims. In some cases the dose could not be increased beyond two or three minims because of reactions. In fact, certain of the more sensitive patients were overwhelmed with the reaction following one minim of this concentrated vaccine.

More recently, therefore, more dilute vaccines have been prepared which contain from twenty-five to fifty million organisms per cubic centimeter. In some very sensitive individuals it has been necessary to provide further dilutions, even as low as ten thousand organisms per cubic centimeter, or less in occasional instances, before the vaccine was tolerated. In most cases, the symptomatic improvement is then definite. A longer course of vaccine injections, with very gradual increase of dosage, is given to these individuals. On the other hand, in those cases with greater tolerance for vaccine, better therapeutic results are often obtained when a somewhat more concentrated vaccine is used, provided the patient does not receive sufficient vaccine to produce a temporary reaction. The dosage should be adapted to the individual. If over-dosage is

avoided, a four-day interval between injections is very satisfactory. A shorter interval is tolerated by some patients. It is difficult to determine the most effective duration of the course of injections, and the desirability or practical necessity of attempting to obtain complete skin desensitization.

Until recently the unaltered vaccine has been used rather than vaccine detoxified with sodium ricinoleate, according to the recommendation of Dorst⁶ and Larson⁸. The more recent experience with detoxified vaccine injected intramuscularly, is already sufficiently under way to indicate advantages. The resulting avoidance or diminution of temporary reactions seems to offer a distinct advantage, both from the standpoint of the patient's comfort, and from that of the therapeutic results obtained, this modification supplementing the effect of reducing the dosage. Certain patients have not tolerated the unaltered vaccine, but have been relieved greatly following treatment with the detoxified preparation.

Dorst's work was limited by giving vaccine therapy alone to a group of patients with chronic irritable colon,

who had received no other type of treatment. It has not seemed justifiable in this work to withhold from these patients the older, comprehensive, therapeutic measures of recognized value, mentioned above. It is common knowledge that the majority of mild and moderate cases of irritable colon will become symptom-free with this program of therapy alone, provided sufficient care is taken in the elimination of the nervous factors.

In order to put vaccine therapy to a more severe test, and to eliminate favorable results not related to this type of treatment, we have utilized a carefully selected group of sixty-eight patients with chronic irritable colon, who had resisted the older therapeutic measures with definite persistence of symptoms. Vaccine therapy, of the type noted above, was introduced then as the only new therapeutic measure, other conditions remaining essentially constant. The practical results of such vaccine therapy upon colon distress, pylorospasm, and the associated symptoms are tabulated statistically in table I. The sixty-eight cases shown in this table have been treated with concentrated and unaltered vaccine. This

TABLE I
Practical Therapeutic Results of Autogenous Stool Vaccine
Injections Upon Symptoms of 68 Cases*

	Colon pain	Pylorospasm syndrome	Constipation	Headache	Vertigo
Number of cases	57	29	34	23	11
Symptoms aggravated	2 (3%)	1 (3%)	0	2 (9%)	0
Symptoms unchanged	9 (16%)	8 (28%)	8 (24%)	8 (35%)	5 (46%)
Slight improvement	8 (14%)	3 (10%)	4 (12%)	1 (4%)	2 (18%)
Moderate improvement	11 (19%)	2 (7%)	4 (12%)	2 (9%)	0
Marked improvement	9 (16%)	2 (7%)	5 (14%)	4 (17%)	1 (9%)
Complete relief	18 (31%)	13 (45%)	13 (38%)	6 (26%)	3 (27%)
Total cases improved	46 (81%)	20 (69%)	26 (76%)	13 (56%)	6 (54%)

*Cases with persistence of symptoms after other therapy, showing results following introduction of vaccine therapy as the only new therapeutic measure. (Undiluted and unaltered vaccine was used in this group of cases.)

provides statistical data for comparison with the results obtained from diluted and detoxified preparations

In the majority of obstinate cases thus treated, the pylorospasm and colon symptoms either improved or disappeared. Included in this group were a few unusually marked cases of pylorospasm, unassociated with colon distress, in which the symptoms had persisted in spite of comprehensive and intensive treatment. Yet these symptoms not infrequently disappeared in a striking manner with the introduction of vaccine therapy. Many of these cases noted marked improvement in their constipation, and were able to discontinue supplementary measures for the relief of this symptom, after vaccine treatment had been instituted. Certain patients, not listed in table I, but presenting a well established diarrhea as the main evidence of colon irritability, were also promptly relieved with vaccine. There were certain patients who had experienced for a long time very distressing headaches of the type often associated with constipation and gastrointestinal distress, not relieved by any of the previous therapeutic measures instituted, but which disappeared under vaccine therapy.

In this connection, it is admitted that in general the objective study of functional symptoms is difficult, and the danger of undervaluating psychological influence is recognized. How-

ever, this group of obstinate cases, whose symptoms had not responded satisfactorily to the previous therapeutic measures, did not represent an enthusiastic group, susceptible to therapeutic suggestion. Furthermore, symptoms as persistent as irritable colon or pylorospasm pain, or chronic headaches, are so stamped upon the individual as to be independent of any mental suggestion. A definite improvement or disappearance of such symptoms is therefore significant.

On the other hand, the symptoms referred to in table II are more purely subjective and less convincing as an index of the effectiveness of vaccine therapy. Even an objective change such as gain in weight is quite dependent upon improvement of appetite. Nevertheless, it was interesting to note that many of these patients, who had complained of chronic fatigability, were enthusiastic about their general improvement, and emphasized particularly the fact that they felt more energetic.

As to the average duration of symptomatic improvement, the above cases have been followed from one to twelve months. This period has been of sufficient duration to demonstrate the practical value of vaccine therapy.

Although vaccine therapy has proved very helpful in the majority of the more obstinate cases with irritable colon and related symptoms, there is evidence that it does not minimize the

TABLE II
Other Results of Vaccine Therapy in Group of 68 Cases

- 1 Appetite improved in 39 patients (57%)
- 2 Gain in weight in 11 patients (16%) (In these patients who gained weight, the average gain per patient was eleven pounds, and occurred with no change in dietary advice as previously outlined)
- 3 Improvement in general feeling of well being occurred in 46 patients (68%) (Improvement very striking in some cases)

therapeutic value or importance of the comprehensive therapeutic program, effective previously in the treatment of the majority of the mild and moderate cases. A major nervous problem which could not be controlled satisfactorily was an outstanding factor in some of the cases, whose gastrointestinal distress and pain were not relieved by vaccine therapy. In certain other cases, whose symptoms were relieved only partially by vaccine treatment, it was found that changing the stool flora was an extremely helpful supplementary measure. The importance of substituting a *diluted* vaccine, in those cases not relieved by a more concentrated preparation, has been emphasized.

Table III summarizes the frequency and degree of skin reaction occurring, with vaccines prepared from different stool organisms, in the total group of patients presenting chronic irritable colon and associated symptoms, upon whom skin tests were carried out. This group of 198 patients included the 68 treated with vaccine and referred to above, and 130 additional patients. The colon bacillus vaccine gave the most marked areas of skin reaction, although there was frequently

marked skin sensitivity to the non-hemolytic streptococcus. Skin sensitivity was less frequent, and usually less marked, when present, with the other organisms isolated. A number of patients were definitely skin sensitive to two or more organisms. The largest areas of skin reaction occurred with the *communior* strain of *B. coli*. In some cases, areas as large as nine or ten centimeters in diameter were seen, with associated injection of the lymphatic vessels leading to the axilla. In Table III the average intensity of the skin reaction, as evidenced by redness and swelling, has been measured on the scale of one to four plus for the various organisms.

In a sub-group of these cases, skin tests were done, both with these autogenous vaccines, and also with the corresponding strain of vaccines, originally prepared from stool cultures in other cases. It was found that the skin reactions in the majority of cases were similar with the autogenous and non-autogenous stool vaccines of the same organism. For example, with the two strains of colon bacillus, 98.5 per cent of the patients giving a positive skin test with the autogenous vaccine also gave a positive reaction with the

TABLE III

Frequency of Isolation from Stools, and Vaccine Skin Sensitiveness, of Common Stool Organisms (in 198 Patients Presenting Symptoms of Irritable Colon, Pylorospasm or Both)

	Frequency of isolation from stool (cases)	Frequency of positive skin reaction when isolated (cases)	Average diameter and intensity of positive skin reactions
<i>B. Coli (communis)</i>	279 (91%)	170 (95%)	4.4 X 4.4 cm + + +
<i>B. Coli (communior)</i>	77 (38%)	74 (96%)	4.5 X 4.5 cm + + +
<i>Streptococcus nonhemolytic</i>	107 (54%)	67 (62%)	2.7 X 2.7 cm + +
<i>Staphylococcus aureus</i>	27 (14%)	13 (49%)	2.4 X 2.4 cm + +
<i>Streptococcus viridans</i>	11 (5%)	4 (36%)	2.8 X 2.8 cm + +
<i>Hemolytic streptococcus</i>	2 (1%)	0	

corresponding nonautogenous preparation. In the case of the nonhemolytic streptococcus stool vaccines, the discrepancy between the skin reactions of autogenous and nonautogenous preparations was considerably greater than with the colon bacillus. This fact may be due to the great variety of strains of the streptococcus. There were occasional cases in which the nonautogenous vaccine gave a positive skin test, and the autogenous vaccine of similar strain produced a negative test.

A control group was carefully selected, which included twenty-one healthy individuals, with no present or past history of symptoms of irritable colon, pylorospasm, or any of the common allergic conditions. In comparing the findings in table IV with those of table III, it is noted that the frequency and degree of positive skin reactions are appreciably less in the control group than in the irritable colon cases. This is particularly true of the three common stool organisms, viz., the two strains of colon bacillus and the nonhemolytic streptococcus. The more infrequent stool organisms are probably chance findings. Their significance may lie in the fact that they come from the mouth, throat or gall

tract. In this control group, positive skin tests occurred almost as frequently in the children as in the adults. The five children included were between five and fourteen years of age.

In table V the degree of skin reaction before, and two weeks after, completion of vaccine therapy was compared in a group of sixteen consecutive cases. It is noted that there was a definite tendency for the skin reaction to decrease in diameter and intensity. A decrease was noted in 75 per cent of the cases, including 12.5 per cent which exhibited a complete disappearance of the skin sensitivity, following vaccine treatment. As to the possibility of parallelism between symptomatic improvement and decrease of skin reaction following vaccine treatment, no final deductions can be drawn from this small group of sixteen cases. In the majority of cases there was some parallelism, but the significance of this finding was rendered questionable by the fact that, in one case, the skin reaction increased after vaccine, although there was marked symptomatic improvement, and, in a second case, there was a similar degree of symptomatic relief, with no change in the degree of skin

TABLE IV

CONTROL CASES

Skin Sensitivity of Twenty-One Normal Individuals, With no Present or Past Symptoms of Irritable Colon, or of any of the Common Allergic Conditions
(Sixteen Adults and Five Children)

Organisms	Frequency of isolation (cases)	Frequency of positive skin reaction when isolated (cases)	Average diameter and intensity of positive skin reactions
<i>B. Coli (communis)</i>	17 (81%)	11 (65%)	3 × 3 cm + +
<i>B. Coli (communior)</i>	13 (62%)	9 (69%)	2½ × 3 cm + +
<i>Streptococcus (nonhemolytic)</i>	14 (67%)	3 (21%)	1 × 1 cm + +
<i>Staphylococcus aureus</i>	2 (9½%)	1 (50%)	1 × 1 cm +

Compare frequency and intensity of skin reaction to individual organisms in this control group with corresponding findings in irritable colon group (table III)

TABLE V

Comparison of Degree of Skin Reaction, Before and After Therapeutic Course of Eight Vaccine Injections (Unaltered Vaccine) (Sixteen Consecutive Cases)

Patients	Skin reaction before treatment	Skin reaction after treatment	Skin reaction decreased*	Skin reaction disappeared†	Skin reaction unchanged	Skin reaction increased
1	4 + (5 × 6 cm)	2 + (3 × 4 cm)	—			
2	3 + (4 × 3 cm)	2 + (3 × 3 cm)	—			
3	4 + (4 × 6 cm)	3 + (3 × 4 cm)	—			
4	3 + (5 × 2 cm)	3 + (5 × 3 cm)			0	
5	4 + (6 × 6 cm)	2 + (3 × 3 cm)	—			
6	4 + (4 × 6 cm)	1 +	—			
7	3 +	No reaction		—		
8	4 + (5 × 3 cm)	1 + (2 × 1 cm)	—			
9	3 + (5 × 4 cm)	2 + (3 × 2 cm)	—			
10	3 + (5 × 3 cm)	2 + (2 × 2 cm)	—			
11	1 + (2 × 3 cm)	3 +				+
12	3 + (4 × 4 cm)	3 + (4 × 4 cm)			0	
13	4 + (6 × 6 cm)	4 + (6 × 7 cm)			0	
14	4 + (5 × 9 cm)	3 + (4 × 4 cm)	—			
15	4 +	2 + (3 × 3 cm)	—			
16	3 + (3 × 4 cm)	No reaction		—		
TOTAL			10 cases or 62½%	2 cases or 12½%	3 cases or 19%	1 case or 6%

*Either decrease or disappearance of skin reaction in 75% of cases

†Some skin sensitivity was still present after vaccine therapy in 87½% of cases

sensitivity This experience is not surprising, however, in view of the existing knowledge regarding marked changes in degree of skin sensitivity, which occur occasionally in various types of allergy, without any treatment having been administered

In almost every instance where vaccine therapy is used with good effect, the question is raised as to whether one is dealing with a specific effect, or with a nonspecific protein reaction This attitude is due mainly to the excellent work of Peterson⁹, Joseph L. Miller¹⁰, and others, who have demonstrated the occurrence of nonspecific protein therapy, its value in various conditions, and the importance of con-

trolling any work that appears to show specific vaccine effects

As regards the nature of the therapeutic action of autogenous stool vaccine treatment in irritable colon and pylorospasm patients, the evidence favoring a specific effect is

1 That there is a marked skin reaction to certain of the isolated stool bacteria in a very high percentage of this irritable colon group of patients,

2 That the best therapeutic results in relieving irritable colon pain seem to occur when systemic reactions are avoided, by using small, rather than large, doses, and by giving the detoxified vaccine, whereas Miller¹⁰ and others have emphasized the im-

portance of obtaining a systemic reaction, preferably with some fever, if satisfactory results are to be obtained from a nonspecific type of therapy

On the other hand, the main point of evidence suggesting a nonspecific protein mechanism is that an appreciable percentage of the *control* group shows skin sensitivity to the common stool organisms. For example, 69 per cent of this group were skin sensitive to the *B. coli communior* vaccine, when this organism was isolated

When one considers the fact that the human race is exposed universally and throughout life to most intimate contact with, and absorption of, disintegrating stool organisms, it is not surprising that an appreciable percentage of the control group was skin sensitive to stool vaccines. It is also a well recognized fact that there are individuals who have never had hay fever symptoms, who, nevertheless, show skin sensitivity to ragweed. This fact, in itself, is not supportive of either specificity or nonspecificity. When the real mechanism of allergy and immunity is discovered, questions of this sort will be answered more definitely.

Recently we have started to treat a control group of irritable colon patients with nonspecific, milk protein injections, as a further check upon the exact mechanism underlying the above therapeutic results in irritable colon cases, but this work is too recent to discuss results at the present time. We are also studying a group of irritable colon patients from the standpoint of their skin sensitivity to various other substances, in an effort to further elucidate the problem.

SUMMARY

1 Autogenous, stool vaccine therapy, utilizing organisms to which the patient is skin sensitive, has been employed in the treatment of a group of patients with obstinate irritable colon and associated symptoms. In order to put vaccine therapy to a more severe test, and to eliminate favorable results not related to vaccine treatment, a carefully selected group of sixty-eight patients has been utilized, who had resisted previously a comprehensive program of the older therapeutic measures with definite persistence of symptoms. Vaccine therapy was then introduced as the only new therapeutic measure, other conditions remaining essentially constant.

2 The most important fact revealed in the above observations has been the demonstration of the definite therapeutic value of properly selected stool vaccines, in partially or completely relieving the remaining symptoms of the majority of these more obstinate irritable colon patients. The above experience has demonstrated that vaccine therapy not only tends to relieve the colon distress and associated symptoms, but also makes it possible for a majority of these patients to tolerate a greater variety of diet and a greater degree of nervous activity, and furthermore, to place less emphasis upon the supplementary measures for the control of constipation.

3 The therapeutic results tabulated statistically in table I were obtained with concentrated and unaltered vaccine, giving an average course of eight injections. The results obtained more recently, with a longer course of more dilute vaccines detoxified with sodium

ricinoleate, and with greater emphasis upon determining the optimum dosage for each individual, have been even more satisfactory than those outlined in table I, and obtained with the original method. The exact statistics with the newer method have not yet been compiled; but certain patients who failed to tolerate the concentrated, unaltered vaccine have obtained symptomatic relief from the more recent method

4 Vaccine therapy *should not displace* the older therapeutic measures of recognized value in irritable colon cases, such as control of various neurogenic factors, proper diet and regulation of bowels, the discriminate use of antispasmodics, and, in some cases, the changing of stool flora. This comprehensive program, with special attention to correction of all faulty habits, should precede vaccine therapy for the following reasons

(A) The symptoms of the majority of the mild and moderate cases will disappear with this comprehensive therapy. Vaccine therapy is not necessary, therefore, in this group

(B) In the obstinate cases, whose symptoms do *not disappear* with the comprehensive program, the colon irritability and spasm, nevertheless, tend to be *partially* reduced by the elimination of aggravating neurogenic factors and other faulty habits. If vaccine therapy is introduced subsequently, as a supplementary measure, the

end results of colon therapy, as well as the general condition of this group of patients, will be more satisfactory than if the comprehensive therapy were to be omitted, and vaccine therapy alone utilized. As the effects of vaccine therapy become apparent, those measures in the comprehensive program which are rendered unnecessary should be discontinued.

5 The colon bacillus was the most frequently isolated organism, and, as a vaccine, gave the most frequently positive and most marked skin reactions. (See table III)

6 Skin sensitivity in a *control* group of healthy, asymptomatic individuals, with no history of any irritable colon or allergic symptoms, was tested. (See table IV) Sixty-five per cent of the control group showed skin sensitivity to one strain of the colon bacillus, and sixty-nine per cent to another strain

7 Skin sensitivity to stool vaccines was shown to decrease and even to disappear, in some irritable colon cases, under vaccine therapy. (See table V)

8 As to the exact mechanism involved in the production of the above therapeutic results of vaccine therapy, evidence is presented for and against a specific vaccine effect. The available evidence does not justify a definite decision upon this question. A control group of patients is being treated with nonspecific milk-protein injections

REFERENCES

¹BARKER, L. F. On the management of the spastic colon and mucous colopathy, especially in hypervagotonic persons, *Am Jr Med Sci*, 1929, clxxviii, 606-615

²BOCKUS, H. L., BANK, JOS., and WILKINSON, S. A. Neurogenic mucous colitis, *Am Jr Med Sci*, 1928, clxxvi, 813-829

³JORDAN, S. M. The irritable colon, *Jr*

- Am Med Assoc, 1929, xciii, 592-595
- ⁴LICHTY, J A The present consideration and care of the colon, Jr Am Med Assoc, 1931, xcvi, 649-653
- ⁵See discussion of Dr Lichty's paper
- ⁶DORST, S E, and MORRIS, R S Bacterial hypersensitivity of the intestinal tract, Am Jr Med Sci, 1930, clxxx, 650-656
- ⁷HARTMAN, F W, and JACKSON, E Isolation, selection and preparation of bacteria for vaccines, to be published in Am Jr Clin Path In press
- ⁸LARSON, W P, and EDER, H Immunization against diphtheria with toxin detoxified with sodium ricinoleate, Jr Am Med Assoc, 1926, lxxxvi, 998-1000
- ⁹PETERSON, W F Protein therapy and non-specific resistance, MacMillan Co, New York, 1922
- ¹⁰(a) MILLER, J L Non-specific therapy, Medicine, 1927, vi, 513-549 (b) MILLER, J L The present status of non-specific therapy, Trans Med Sec, Jr Am Med Assoc, 1930, vol 95, 464-468

On the Advantages of Being Ill

“TO BE ill, or to undergo an operation, is to be initiated into the mystery of nursing, and to learn the comforts and discomforts of an invalid's life, the unearthly fragrance of tea at daybreak, the disappointment of rice pudding when you thought it was going to be orange-jelly, and the behavior of each constituent part of the bedclothes You know, henceforth, how many hours are in a sleepless night, and what unclean fancies will not let us alone when we are ill, and how illness may blunt anxiety and fear, so that the patient is dull, but not unhappy or worried, and how we cling to life, not from terror of death, nor with any clear desire for the remainder of life, but by nature, not by logic In brief, you learn from your own case many facts which are not in text-books and lectures, and your patients, in the years to come, will say that they prefer you to the other doctor, because you seem to understand exactly how they feel I wish you therefore, young man, early in your career, a serious illness, or an operation, or both For thus, and thus alone, may you complete your medical education, and crown your learning with the pure gold of experience The crown of experience is like the crown of Lombardy, a band of iron set in a band of gold and it is believed, even now, by some people, that the iron of that crown is more valuable than the gold”—From *Confessio Medici*, by STEPHEN PAGET, F R C S (The Macmillan Company, New York City, 1931, Reissue)

Diagnostic Value of Secretory Function in Gastric Disease: Various Methods Studied and Compared*†

By ERNEST H. GAITHER, M.D., F.A.C.P., *Baltimore, Md*

DURING the past few years, renewed and continued interest has been manifested by numerous investigators in the domain of gastric secretion, and the test which has apparently met with almost universal favor has been that in which histamine, subcutaneously administered, has been used as the stimulator of gastric gland activity.

A careful survey of the current literature on this subject reveals the interesting fact that practically all observers agree as to the direct action of this drug upon the gastric glands, or upon a mechanism which has intimately to do with their secretion, innumerable tests of acidity have satisfied many workers in this field that a study of the acid values by means of the histamine test, will enable one to form an excellent and reliable idea as to the ability of the glands to secrete acid, and will furnish information of true diagnostic worth.

Immediately after the successful application of the histamine test for acid

determination, certain investigators entered upon a searching inquiry into the matter of enzymes, chlorides, and other constituents, and, as was to be expected, conflicting claims, either hostile or extravagantly favorable in nature, were made as to the dependability and diagnostic value of the test in the presence of disease under varying conditions. Because of these conflicting and unsatisfactory views, it was decided to confine the present investigations to a consideration of acid values only.

The proponents of the histamine test state that its advantages are not only the subcutaneous application which eliminates the disturbing psychic factor induced by the mastication of solids and the swallowing of liquids as in other test meals; but also the fact that the dosage may be standardized and pure juice obtained. Then, too, because of the direct action of this substance on the gastric glands, many cases which show achylia by other test meals will give an acid response after the injection of histamine.

Objections to the Ewald, alcohol, and various other test meals, have been presented by some observers, who claim that contamination and dilution

*Read before the American Gastro-Enterological Association, Atlantic City, May 5, 1931.

†From the Gastro-Intestinal Clinic of Johns Hopkins Hospital, Baltimore.

of the gastric content are so engendered by the introduction of these substances, as to mask the true secretory power of the gastric glands, they aver, also, that the neutralization of the hydrochloric acid by saliva, food, and regurgitation of duodenal contents further complicates an already deceptive result. The contention is advanced that tests other than the histamine injection do not provide sufficient stimulation to obtain an adequate response from the gastric glands.

I am unable to accept these objections as valid, some of them would appear to be mere sophistry. For instance, it can certainly be proven that in the majority of cases, bread and water supply an adequate stimulation to gastric gland secretion, and as for the argument regarding neutralization by swallowed saliva and regurgitation of duodenal contents, as well as that concerning contamination brought about by solids and liquids, does not such a process more nearly simulate the usual physiologic routine of digestion? And after all, are we not endeavoring to ascertain the functional capacity of the gastric glands under conditions as nearly physiologic as possible? No one can gainsay the fact that Nature never depends upon histamine injections to bring about a normal response of the gastric secretory glands.

This study represents an investigation by three methods, using the fractional extraction

I THE ALCOHOL TEST MEAL

Technique Patient given fifty c c of an 18 per cent alcohol solution containing 0.005 gm phenolphthalein

II EWALD MEAL

Technique One slice of white bread without butter, and one glassful of cool water, ingested forty-five minutes before extraction

III HISTAMINE TEST

Technique Dissolve one histamine tablet of 0.005 gm in three c c distilled water, multiply the weight of the patient by 0.005, this gives the number of c c of histamine solution to be administered subcutaneously

In estimating acidities we made use of the accepted figures of twenty to forty degrees for free hydrochloric acid, and forty to sixty degrees for total acidity, as indicating normal limits, realizing that the acidities following histamine stimulation are considerably higher.

This would seem the opportune moment for stressing two important points, first, in selecting this series of cases for research, every available method of investigation was brought into use in order to insure the absolute correctness of each diagnosis, second, we were not prejudiced for or against any of the methods, and were eager to consider all evidence and all established facts judicially and in order, so as to reach if possible, a correct and unbiassed conclusion as to the diagnostic value possessed by any of the methods.

The cases were grouped under the following headings

- 1 Achylia gastrica
- 2 Adhesions (postoperative, plastic gastric operations)
- 3 Colitis
- 4 Gastric neurosis

5. Hepato-biliary pathology (cholecystitis; cholelithiasis)

6 Ptosis and atony

7 Peptic ulcer

ACHYLIA GASTRICA

We charted in this group all those cases showing in any of the tests a lack of free hydrochloric acid, and have included all such cases from the various groups. There were nineteen in this group

8 Achylia by all three tests

6 Achylia by alcohol, normal or hypochlorhydria by histamine and Ewald

3 Achylia by alcohol and Ewald, normal or hypochlorhydria by histamine

1 Achylia by histamine and alcohol, hypochlorhydria by Ewald

1 Achylia by histamine and Ewald; hypochlorhydria by alcohol

19 Total

These results indicate that a small majority of cases showing achylia by the Ewald and alcohol tests will present free hydrochloric acid after histamine stimulation

ADHESIONS (POST OPERATIVE)

There were five in this group.

4 Hyperchlorhydria by all three tests

1 Achylia by alcohol, normal by Ewald and histamine

5 Total

In this group the histamine shows no diagnostic advantage over the Ewald and alcohol tests

COLITIS

Six were included in this group

2 Hyperchlorhydria by all three tests

1 Normal acidity by all three tests

1 Moderate hyperacidity by histamine, normal by Ewald and alcohol

1 Hyperacidity by histamine, achylia by Ewald and alcohol

1 Hypochlorhydria by histamine and Ewald, achylia by alcohol

6 Total

In this group there is certainly no outstanding advantage of the histamine test

GASTRIC NEUROSIS

There were twenty-five in this group

10 Hyperacidity by all three tests

10 Hypochlorhydria and normal by all three tests

2 Hyperacidity by histamine; normal or moderate hypochlorhydria by alcohol and Ewald

2 Achylia by histamine, normal by alcohol and Ewald

1 Achylia by Ewald and alcohol, hypochlorhydria by histamine

25 Total

This survey shows that in the great majority of cases all three fractional studies coincide. The labile character of gastric secretion is emphasized

HEPATO-BILIARY PATHOLOGY

Twelve in this group

5 Hyperacidity by all three tests

2 Achylia by all three tests

1 Hypochlorhydria by all three tests

- 1 Achylia by alcohol, hypochlorhydria by histamine and Ewald
- 1 Normal by alcohol, hyperchlorhydria by histamine and Ewald
- 1 Normal by Ewald, hypochlorhydria by alcohol, moderate hypochlorhydria by histamine
- 1 Normal by histamine and Ewald, achylia by alcohol

—
12 Total

The histamine presents no diagnostic advantage in this group

PTOSIS AND ATONY

Twelve in this group

- 1 Achylia by all three tests
- 6 Hyperchlorhydria by all three tests
- 2 Hyperchlorhydria by histamine, normal by Ewald and alcohol
- 1 Normal by histamine, achylia by alcohol, hypochlorhydria by Ewald
- 1 Normal by alcohol, achylia by Ewald, hyperchlorhydria by histamine
- 1 Achylia by alcohol, hypochlorhydria by histamine and Ewald

—
12 Total

Histamine here gives no advantage from a diagnostic standpoint

PEPTIC ULCER

Thirty in this group

- 20 Hyperchlorhydria by all three tests
- 1 Normal by all three tests
- 1 Hyperchlorhydria by histamine and Ewald, hypochlorhydria by alcohol
- 1 Achylia by histamine and alcohol, hypochlorhydria by Ewald

- 1 Achylia by Ewald, normal by alcohol, hyperchlorhydria by histamine
- 2 Normal by alcohol and Ewald, hyperchlorhydria by histamine
- 1 Normal by Ewald and histamine, hypochlorhydria by alcohol
- 1 Normal by alcohol and histamine, hypochlorhydria by Ewald
- 1 Normal by alcohol, hyperchlorhydria by histamine and Ewald
- 1 Normal by Ewald, hypochlorhydria by alcohol, hyperchlorhydria by histamine

—
30 Total

The superiority of histamine is certainly not proven in this group of cases

SUMMARY

This investigation was instituted for the purpose of determining whether the histamine test is possessed of outstanding superiority over other methods of estimating the acid values in gastric secretion

One hundred cases were selected—a cross-section of dispensary patients—and in these cases every available method was used in order to insure proper diagnosis. In each case three tests—histamine, Ewald, alcohol, using the fractional method—were applied

The results so obtained are tabulated and reviewed, with the following conclusions drawn

1 The Ewald and alcohol meals are effective stimulators of gastric secretion

2 The objection that the swallowing of saliva, the contamination and neutralization of gastric juice by the meal itself, and also the regurgitation of duodenal contents, markedly or ef-

fectually mask the results of these meals *is not sustained*

3 The labile character of gastric secretion is proved

4 Histamine does in a number of cases offer an advantage in establishing the fact that the glands do possess the power of acid secretion when after the Ewald or alcohol test an achylia would seem to be present

5 The alcohol meal is not nearly so potent a stimulant of gastric gland secretion as the Ewald meal

6 There is ample justification for the continuance of the Ewald meal as a dependable test for gastric gland secretion

7 The claim that histamine is vastly superior to the Ewald meal as a stimulant of acid secretion of the gastric glands has been disproved

8 It would really appear that the application of bread and water as a test of gastric gland secretion is more physiologic than the subcutaneous application of the foreign body, histamine, and that it presents a result more in keeping with normal bodily economy

I wish to add a note of appreciative thanks for very valuable assistance so ably rendered by Miss Stearns, Miss Lesser, and Miss Kravetz, of the Gastro-Intestinal Clinic of the Johns Hopkins Hospital in making the tests used in this investigation

The Clinical Significance of Choroidal Tubercles*

By R T PATON, M D, *Baltimore, Md*

BEGINNING about four years after the discovery of the ophthalmoscope we find descriptions of choroidal tubercles in the medical literature. Among the investigators who are associated with these early observations are Jaeger, Von Graefe, Leber, Manz, Bouchert, Gerlach, Fraenkel, and Horner. These descriptions included the two types commonly known as (1) the granuloma or solitary tubercle, (2) choroidal miliary tubercles. The former is usually associated with chronic tuberculosis, and the latter with acute miliary tuberculosis. These observations have been substantiated by later investigators.

Studies of pathological material have shown that the usual number of tubercles in one eye is three or four, but in some cases there may be a much larger number. Morton reported as many as 70, Parsons, 60-70, Cohnheim, 52, and Boch, 49. The size varies from 0.4 mm to 5 mm. Groenouw stated that tubercles smaller than 0.6 mm could not be seen with the ophthalmoscope.

Some observers claim that miliary tubercles are frequent in general miliary tuberculosis. Cohnheim found

them in every instance in the 18 patients he examined, Boch in over 80 per cent, and Carpenter and Stephenson in 50 per cent, while Marple on repeated and careful examination found the appearance of tubercles to be the rule and not the exception. Marple's earlier investigations gave a very small percentage, but this error he discovered was due to failure to make frequent examinations, especially in the late stages of the disease.

Groenouw in a series of cases, including 378 cases of miliary tuberculosis and tuberculous meningitis, found tubercles of the choroid present in 35 per cent of the cases examined either during life or at autopsy. In 222 cases of the series tuberculous meningitis was the clinical and pathological diagnosis, 44 per cent showed tubercles of the choroid. In contrast with these statistics are the figures given by Bredech. Bredech, 1916, after examining the evidence presented by reports, in which careful examination of the fundus had been made, collected a total of 226 cases of tubercular meningitis, in which 14.6 per cent showed tubercles of the choroid. No doubt these percentages would have been somewhat higher had pathological studies been made in every case. He thought that the number would have reached 20 per cent had there also been more frequent examination of the eyes.

*From The Fifteenth Annual Clinical Session at The Wilmer Ophthalmological Institute, of the Johns Hopkins University and Hospital, Baltimore, Md., March 26 1931.

The diagnosis of choroidal miliary tubercle is dependent to a large extent upon the rapid and unexpected appearance of the tubercle. This fact has been stressed by Fraenkel, Groenouw, Lotin, Weis, and many others. Marple reported a case in which an ophthalmoscopic examination, made at 6 P. M., did not reveal the presence of a tubercle, but four hours later a tubercle appeared. Moore reported one developing in five hours, while Strider and Weis saw tubercles develop in 12 hours. The discrepancy among various authors as to the existence of tubercles, especially in meningitis, is probably due to two factors: (1) Difficulty in examination—tubercles in these cases are usually found only in the terminal stages. (2) Failure of repeated and careful examination. Tooke reported choroidal miliary tubercles in one case as early as 33 days, but in the majority of cases they did not appear until about three days before death. The clinical examinations in all these cases were verified by post mortem examinations.

Both eyes should be examined. Cohnheim found tubercles in both eyes in 15 out of 33 cases examined. These observations were verified by autopsy and microscopic study.

The presence of miliary tubercles of the choroid is often a valuable aid before the laboratory tests have been completed, in making a diagnosis in cases suspected of being typhoid fever, meningitis or miliary tuberculosis. Series of cases, in which the value of the ophthalmoscopic examinations is proved, have been published by Bollach, Hillernan and Laporte. Van der Hoeve reported a case of mastoiditis with cerebral symptoms, in

which the existence of miliary tuberculosis had not been suspected until the ophthalmoscopic examination revealed the presence of miliary tubercles. The diagnosis was confirmed at autopsy.

The prognosis in miliary tubercles of the choroid is nearly always bad. Usually there is a meningitis. Jessup, in a series of 15 cases, in which there were tubercles of the choroid present, found that 14 had tuberculous meningitis. Only one case was free from meningeal complications. The clinical diagnoses were confirmed by post mortem examinations.

Solitary or conglomerate tubercle of the choroid is a rare and destructive disease, and is probably always secondary to tuberculous disease in other parts of the body. The affection is usually unilateral, though bilateral incidence has been reported and verified by post mortem studies. The condition is usually seen in the early years of life, but its occurrence has been reported as late as 62 years (Nedden).

Differential diagnosis is often difficult, for we have to distinguish the tubercles from the various malignant growths, such as glioma, retinoblastoma, detachments with massive exudates, etc. In some cases the diagnosis can be made only after the eye has been removed. If the diagnosis is made, enucleation is not indicated unless all therapeutic measures, especially tuberculin, which in recent years has appeared to act favorably in many cases, have failed.

The results of the study of a case of miliary tubercles, which was recently observed, may be of interest.

The patient, a 10 year old boy, was ad-

mitted to the Harriet Lane Home 12 days after the onset of the illness. There was no history of tuberculous contact. On admission the patient was acutely ill. The chief symptoms were headache, nausea, vomiting, drowsiness and mild diarrhea. The boy was temporarily isolated and treated as a case of typhoid. The eye examination made on admission gave the following results:

There was slight suffusion of the conjunctiva, dilated pupils, and slight photophobia. The patient's general condition became progressively worse. Laboratory tests at this stage gave practically negative results. These tests were repeated two days later. Lumbar puncture showed 290 cells per cc., fluid was under pressure, and a

pellicle was formed on standing. The ophthalmoscopic examination revealed slight bilateral optic neuritis with subretinal exudate forming adjacent to the papillae. The veins were engorged and there was definite retinal edema extending out toward the periphery. The diagnosis of tuberculous meningitis was established on the following day, 16 days after the onset of the illness, when tubercles were visible in both eyes. Ocular examinations had been made three or four times a day, so that it is not likely that tubercles had formed earlier in the course of the disease. The patient died two days later. The pathological diagnosis finally established was miliary tuberculosis with meningitis. Tubercles were formed in practically all organs of the body.

BIBLIOGRAPHY

- JAEGER, E. Über Choroidealtuberkel, Oesterr Ztschr f Prakt Heilk, 1855, Jahrgang, 1, 9-10.
- VON GRAEFE, A., und LEBER, T. Über Aderhauttuberkeln, Arch f Ophth, 1868, xiv, 183-206.
- MANZ, W. Tuberculose der Choroidea, Arch f Ophth, 1858, iv, Part 11, 120-126.
- BOUCHUT, M. Des tubercles de la choroïde et de la rétine pouvant servir au diagnostic de la tuberculose cérébrale, Gaz des Hôp, 1869, 11.
- FRÄNKEL, B. Weitere Beobachtungen von Aderhauttuberkeln, Berl klin Wchnschr, 1869, vi, 37-39.
- HAAB, O. Die Choroiditis tuberculosa chronica, Arch f Ophth, 1879, xxv, 221-236.
- PARSONS, J. H. Diseases of the eye, 1930, Macmillan Company, New York, 539.
- COHNHEIM, J. Über Tuberculose der Choroidea, Virchows Arch f path, Anat, 1867, xxxix, 49-69.
- GROENOUW, A. Beziehungen der Allgemeinerkrankungen und Organerkrankungen zu Veränderungen und Krankheiten des Sehorganes, Handbuch der Augenheilkunde, 1920, Dritte Auflage, 1074-1087.
- CARPENTER, G., and STEPHENSON, S. A case of tubercle of the choroid presenting certain clinical and pathological peculiarities, Ophthalmoscope, 1905, 111, 374-380.
- MARPLE, W. B. Tubercle of the choroid in tuberculous meningitis, Ophthalmoscope, 1912, x, 559-563.
- BREDECK, J. K. The choroidal tubercle in tuberculous meningitis, Am Jr Ophth, 1916, xxxiii, 1-8.
- LOTIN, A. Über die tuberkulose disseminierte Choroiditis und über die Miliartuberkeln der Aderhaut, Klin Monatsbl f Augenh, 1925, lxxiv, 262.
- WEIS, L. Über die Tuberkulose des Auges, Arch f Ophth, 1877, xxiii, 57-158.
- TOOKE, F. Tuberculous meningitis with special reference to the tubercle of the choroid and its pathological manifestations, Tr Am Ophth Soc, 1915-16, xiv, 218-232.
- BOLLACK, J., HILLEMANN, P., and LAPORTE, A. Tubercule miliaire de la choroïde, Annales d'Oculistique, 1927, clxiv, 660.
- VAN DER HOEVE, J. Examen du fond de l'oeil dans la tuberculose miliaire, Bull Soc de pediat de Paris, 1925, xxi, 511-514.
- JESSOP, W. H. A discussion of intra-ocular tuberculosis, Brit Med Jr, Sect Ophth, 1925, 11, 430-433.
- RANDOLPH, R. T., and SCHMEISSER, H. C. A clinical and pathological study of two cases of miliary tubercles of the choroid, Tr Am Ophth, 1915-16, xiv, 585-592.

Laboratory Methods in Clinical Medicine*

Report of Three Cases

- (1) Diaphragmatic Eventration
- (2) Chronic Nephritis without Hypertension, Cardiac Hypertrophy or Retinal Changes
- (3) Unusual Case of Cholelithiasis

By SAMUEL LEVINE, M D, *Brooklyn, N Y*

FROM time to time the statement is made at medical meetings and in the medical press that the introduction of laboratory methods in the practice of medicine has impaired the physician's powers of observation and his clinical sense, and that, as a result of this, his diagnostic abilities have deteriorated and both patient and physician are thereby the losers

It must be admitted that there is some truth in this statement. The keen sense perceptions of the animal, so important in its struggle for existence, are very much diminished in civilized man (Darwin¹). In his struggles he has developed tools of far greater effectiveness than instincts and sense organs. As a result, these are used much less and have therefore lost some of their power. The fact, however, is that man with his duller perceptions has conquered the animal kingdom, and that portion of mankind that wields the technical power of Western civilization dominates all those races that still retain the primal keenness of their senses

Formerly, the physician, in the practice of his art, was forced to rely upon his senses only, which were consequently developed to a fine degree. But this was due to necessity, not to choice. At present, more accurate methods have replaced them to a certain extent. The thermometer registers changes in temperature much better than the thermesthetic sense; the hemoglobinometer and hemacytometer are much more reliable in the study of blood diseases than the naked eye; and general clinical impressions based upon empirically acquired knowledge have given way to tests based upon scientifically controlled facts. It is doubtful whether these have already resulted in dulling physicians' senses. That the progress of medicine along present lines may have such an effect is very likely. The senses of the physician are no exception to the biologic laws of use and disuse (Darwin²). Nor is this fact to be deplored any more than the general lessening of sense acuity in the entire human race, particularly in its civilized portion.

*Received for publication, June 5, 1931

The following cases illustrate the

value of laboratory methods in clinical medicine

DIAPHRAGMATIC EVENTRATION

History Mr N S, aged 31, automobile mechanic, came to my office Nov 15, 1927. His wife and three children were alive and well. He did not use alcohol and smoked twelve to fifteen cigarettes a day. He had had the usual diseases of childhood. At the age of ten, he was very ill and was confined to bed for a year. The late Dr Robert Schultz, who treated him during that illness, informed me that, "When ten years of age, Mr S was ill with abdominal cramps, diarrhea and vomiting. He lost a lot of weight. Diagnosis was tuberculous peritonitis. He was confined to bed for one year and made a good recovery."

Present Illness In the preceding July, during lunch hour, he was standing in front of the garage where he was employed. The car on which he had been working that morning was raised on a jack in the street near the sidewalk. He saw a truck come along and strike the car, throwing it off the jack. No one was injured. "I said nothing, but in the evening, I felt faint and something was pumping in the left side of my chest." Here he pointed to precordium and left axilla. "I had difficulty in breathing and developed a crampy feeling in my left armpit." Then the following symptoms developed: heartburn, relieved by bicarbonate of soda, not relieved by food, sour eructations, and abdominal cramps after meals. There was numbness in left upper and lower extremities, and in front and behind left ear. He had nightmares and dreamt he was falling from some great height. Patient had to give up his position and went to the country for a rest, without any improvement in his condition.

Examination The patient was a medium-sized, hairy male. He had two accessory rudimentary mammae on each side, below and to the inner side of the normally placed mammae, undeveloped and adherent lobules of both ears, and a remarkably large penis. The pulse rate was 72. The blood pressure was 126 systolic and 60 diastolic

in both arms. His weight was 125 pounds (56.8 Kg). Dull tympany was present below left scapula with diminished vocal fremitus and absent breath sounds. After radiographic examination and when *purposefully looked* for, the following were noticed. When stomach was empty, there was dull tympany at the base of the left lung and the heart was only slightly displaced to the right. When the stomach was full, the heart was much more displaced to the right (Assman²), and the base of the left lung was flat. Splenic dullness could not be elicited because of marked tympany in that area. The left lower chest was flattened, more so over precordium. While the chest expanded with inspiration in a normal manner, the intercostal spaces retracted, particularly over precordium.

Radiographic examination showed that the left dome of the diaphragm was high and moved slightly downward with inspiration. The heart was displaced to the right (figure 1). Barium gruel was then administered. Fluoroscopy of stomach revealed that the greater part of it was situated under the lower left ribs. The air bubble was large. The fundus rested against the diaphragm. Body and pylorus were situated in the left side of abdomen. The incisura angularis was absent and the pyloric part ran straight downward. The duodenum was pulled over to the left. The stomach emptied rapidly (Figure 2).

A barium enema was given and it was noticed that the hepatic flexure of the colon formed an obtuse angle and the transverse colon ran upward and to the left (figure 3).

Cholecystograms taken after the administration of tetra-iodophenolphthalein by mouth, revealed the gallbladder faintly outlined and with poor concentration. This was probably due to the abnormal position of the duodenum which interfered with the normal function of the papilla duodeni.

Proctoscopic and sigmoidoscopic examinations were negative. Urinalysis was negative. Two out of three specimens of feces gave a faintly positive reaction to the benzidine test. Blood examination was negative except for an increase in the icteric index which was 107, probably caused by the displacement of the duodenum which interfered

with the patency of the common bile duct. The blood Wassermann reaction was negative and the blood count was normal.

COMMENT

This man was seen by several good clinicians, who, in view of the history and symptoms made a diagnosis of neurosis. Some of them also thought that he had a lesion in the left lung.

These patients are usually diagnosed as neurotics and psychopaths. Friedrich Schneider in 1900, the first man with diaphragmatic eventration to be studied with the roentgen rays, told Dr. Hirsch⁴ "Many doctors did not believe that I suffered." Leichten-

stern's⁵ patient with diaphragmatic hernia was considered by him as a "simulant", a neurotic, and he really acted as such. This has also been the experience of Carman and Fineman⁶, Soresi⁷, Funk⁸, and Funk and Manges⁹. Walton¹⁰ writes, "During the past ten years, there have been more authentic cases of eventration reported than in the previous 139 years, when Petit first reported his case." "Clinically", says Hitzengerber¹¹, "this diagnosis can only be surmised, without the aid of the roentgen rays, it can hardly ever be made." During eight years in a very active radiographic

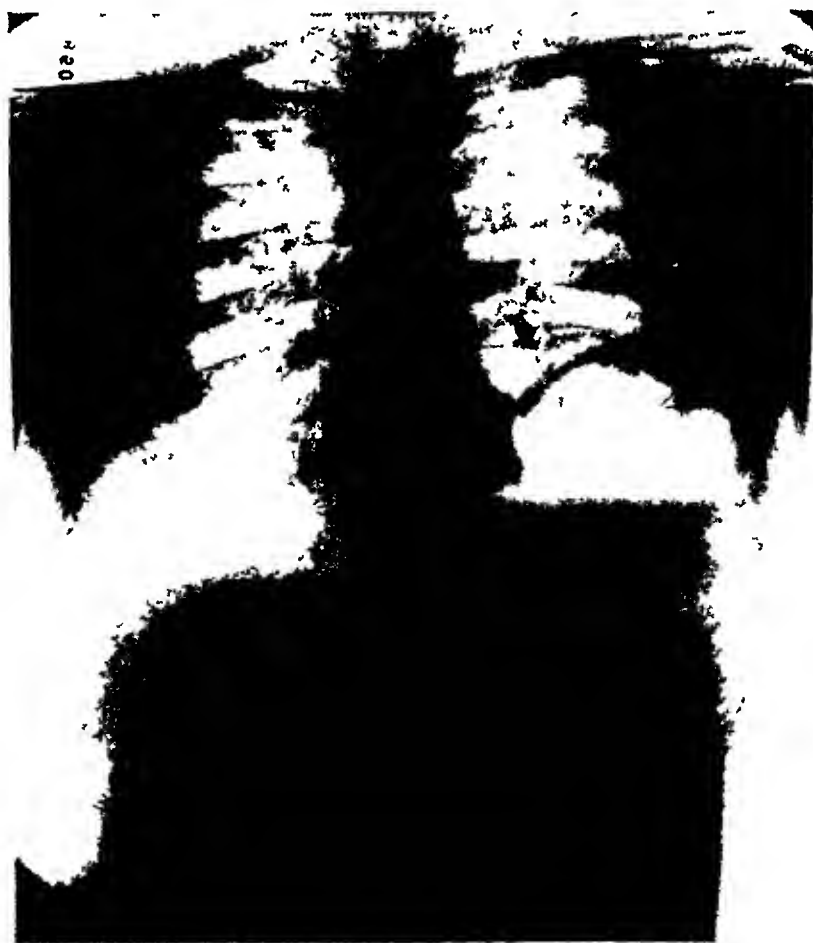


FIG. 1. Case 1. Left dome of diaphragm high. Heart displaced to the right. This film was made one hour after dinner.

service he saw twenty cases of eventration. So many cases have been reported in recent years that Hitzenger thinks it is fortunate that not all observed cases are published.

It is of real clinical importance to recognize this condition because a mistaken diagnosis may have serious consequences. Since the physical signs in the lung strongly suggest the presence of fluid, a needle may be introduced which would enter the stomach with, perhaps, fatal results (Pepper¹², Stilvelman¹³, Clopton¹⁴, Allan¹⁵).

The question now arises whether his long illness at the age of ten was

not due to diaphragmatic eventration. It is idle to speculate now, but it is very likely, in view of the protean manifestations of this disease and its periods of complete freedom from symptoms, that a diagnosis of tuberculous peritonitis would have been changed to diaphragmatic eventration, had the roentgen rays been used at that time.

* * *

CHRONIC NEPHRITIS WITHOUT HYPERTENSION, CARDIAC HYPERTROPHY OR RETINAL CHANGES

History Miss R Z, aged 23, single, came to my office May 11, 1929. She was employed in a candy factory up to two years



FIG 2 Case 1 Esophagus, stomach and duodenum. Note position of cardia and large air bubble.

ago, since then she has assisted her mother in her household duties. Menstruation began at the age of sixteen and occurred every twenty-eight days, lasting three days. Habits normal. She had had the usual diseases of childhood including diphtheria and scarlet fever, for the latter of which she was kept in a hospital for contagious diseases for three months.

The patient, as well as her mother, denied that she had ever had kidney disease or that she was ever edematous. Her tonsils were removed two years before, and up to that time she had had frequent attacks of sore throat. The appendix was removed five years ago. Eight months before, she experienced dull pain in the epigastrium which was not severe and did not radiate. This pain had no relation to meals and was not relieved by vomiting or by bowel movement.

Occasionally, she awakened at night with pain. During the first month of illness she vomited soon after meals, even the sight of food produced vomiting. Since then, she has vomited only at rare intervals, mostly in the morning before breakfast. The color of the vomitus was that of the food ingested. She had severe heartburn which was relieved by an alkaline water. She belched a great deal and there was a sense of heaviness in epigastrium. Her appetite had been poor throughout her life. During this illness, she had lost thirteen pounds. Her bowels were quite regular up to nine months before, since which time she has taken a daily enema or cathartics. No blood or mucus was noticed in the stools. Nocturia, frequency or dysuria, cough or dyspnea on exertion had not been noted. There was an occasional slight headache, no dizziness or



FIG 3 Case 1 Colon and stomach filled simultaneously

visual disturbances. She slept quite well but for the epigastric pain.

Examination The pulse rate was 108, blood pressure, 110 systolic and 80 diastolic in both arms. The weight was 86½ pounds (39.3 Kg). The patient was a thin, narrow individual, and her face was grayish-pale, the thyroid gland enlarged, no thrill felt or bruit heard over it, there was marked tremor of both hands, no exophthalmos present, Graefe and Moebius signs were absent, no hypersensitive skin zones present. Liver and spleen not palpable. The abdomen presented a scar due to appendectomy. There was marked epigastric tenderness.

A casual specimen of urine gave a slightly alkaline reaction, the specific gravity, 1010, a moderate amount of albumin, no sugar, microscopic examination, negative. Two blood-chemistry examinations were done in an interval of four days and gave the following results: Urea nitrogen, 16.6 to 19.2-3 mgms, creatinine, 4.3 to 4.5, sugar, 108.1 mgms, icteric index, 5, blood Wassermann reaction was negative. A urine concentration test was then carried out. The patient brought two specimens taken at 8 a.m. and 10 a.m., of which the specific gravity was 1009 and 1010 respectively. Two blood counts were taken in a four days' interval and showed 62 per cent to 57 per cent hemoglobin (Sahli), 3,500,000 to 3,100,000 red blood cells, 9,400 to 7,400 white blood cells. The differential count showed 54 per cent polymorphonuclear leukocytes, 27 per cent small and large lymphocytes, 2 per cent transitionals, 12 to 17 per cent eosinophiles. The red blood cells were very pale. There was considerable poikilocytosis and anisocytosis and an occasional microcyte was seen.

In view of the persistence of eosinophilia, the stool was examined for ova. We observed structures which suggested to us the ova of *Uncinaria americana*. In order to check up on the diagnosis of a disease with which we were not familiar, we had arranged to send the stool to a competent parasitologist who had a great deal of experience in tropical diseases. Unfortunately, the patient's relatives refused to cooperate. Perhaps it ought to be mentioned that this patient had never visited a tropical country. The benzidine test was negative. There was free hy-

drochloric acid present in the gastric contents.

The eye grounds were examined by an ophthalmologist who found "both fundi entirely negative."

Radiographic examination revealed no abnormalities in heart and lungs. A barium test meal was then administered. There was no evidence of organic disease in stomach or intestines. There was considerable gastrop-tosis, stomach reaching 12 cm. below the crest of the ileum, duodenal stasis was present to a considerable degree. After five hours both stomach and duodenum were empty.

The patient died eleven months later.

COMMENT

This patient had been treated for six months for gastric ulcer by an eminent gastroenterologist, thoroughly acquainted with his specialty and on the teaching staff of a large university. Nevertheless, a blood urea done by a competent technician would have done more to point towards a proper diagnosis than all the experience and learning of this clinician. The presence of albumin in the urine does not have the same significance as the high urea in the blood. Had this patient presented all the classical symptoms of chronic nephritis, the clinical diagnosis would have been evident and laboratory methods might have been dispensed with or only used to corroborate it. However, this was an atypical case (Bannick¹⁶, Bennett¹⁷, Fishberg¹⁸), and offered little, if any, clinical evidence of the true condition. Here, the clinical laboratory, impersonal and objective, made the diagnosis.

* * *

UNUSUAL CASE OF CHOLELITHIASIS

History Mrs. S. L., aged 55, born in Russia, came to my office, Jan. 10, 1929. She

had been married 36 years and had never been pregnant. The menopause set in ten years before. When in Russia, she had the following diseases: pneumonia at the age of 18, malaria at 25, cholera at 29 and typhoid fever at 36. She had had two minor operations on the uterus per vaginam, one at 27, and the other when 30 years of age. Their exact nature could not be determined. At 40 she was operated upon for an ischio-rectal abscess, at 46 a left intraligamentous cyst was removed. One year before, she had an attack of severe cramps and pressure in epigastrium, which radiated to the back, was worse after meals, but was relieved by bowel movements. The pain was so severe at times that it kept her awake at night. Within the last month she had lost nine pounds, and in the preceding eleven months, twenty-one pounds. She was never jaundiced.

Examination There was definite and constant tenderness and rigidity in the right upper quadrant of the abdomen. Rocking the liver caused much pain. The history and physical findings were so typical of cholelithiasis that this diagnosis was made on clinical grounds by Dr. Joseph Rivkin who first saw this patient. I readily concurred in the diagnosis.

Examinations of urine, feces, gastric contents and blood were negative.

A barium test meal was administered. Radiographic examination of gastro-intestinal tract revealed a normal stomach, duodenal cap was indented at its outer border by an oval mass and a dense tube projected from the lower part of this mass (figure 4). After five hours, the stomach was almost empty, but the oval mass with the tube remained unchanged and continued so on the twenty-four, forty-eight and seventy-two hour plates.



FIG. 4. Case 3. Duodenal cap is indented at its outer border by an oval mass. A dense tubular-appearing shadow projects from the lower part of this mass.

Cholecystograms were taken sixteen hours after administration of tetra-iodophenolphthalein by mouth. The gall bladder was not visualized and only the structures described above were seen. Roentgenograms were then taken twelve days, four weeks and six weeks later. The findings remained unchanged up to the six weeks' plate when a slight change was noticed (figures 5 and 6).

Interpretation of the plates was difficult. It was thought that a duodenal diverticulum was present. However, since the symptoms continued, patient submitted to an operation which was performed by Dr. John Linder at the Brownsville and East New York Hospital. The operative findings were as follows: The dense, tubular structure represented the lower part of the gall bladder which was tightly filled by a lime cast. The

oval mass above it represented the upper part of the gallbladder and was tightly filled by a large cholesterol stone.

COMMENT

In this case the clinical diagnosis was correct while the roentgenograms only served to confuse us. This much must be admitted. The real fault, however, did not lie with the method but with its incorrect application. Had I taken a plain plate of the abdomen *before* administration of barium, a duodenal diverticulum scarcely could have been suspected, and the diagnosis of gallstones would have suggested itself. Renal stones could have been ex-



FIG 5 Case 3. After twelve days, the oval mass and dense tubular shadow remain unchanged.

cluded, if necessary, by pyelograms. Furthermore, had this precaution been taken, the exact size and shape of the stones could have been predicted accurately, whereas, clinically, this was impossible. It is therefore clear, from this case, that in the radiographic examination of the abdomen, no barium is to be administered before a study is made without it.

CONCLUSIONS

Laboratory methods in clinical medicine have recently been subjected to severe criticism on the ground that they tend to impair the physician's

powers of observation and his clinical sense. In defense of these methods I wish to emphasize (1) that they are an extension of the clinician's senses, a gain far outweighing any possible loss of sense acuity, (2) that the careful application of these methods is responsible for most of the progress we have made, and (3) that they are not intended to replace older clinical procedures.

The shortcomings of the laboratory are undeniable. These can be overcome only by giving further attention to their improvement, and not by reverting to the sole use of the unaided



FIG 6 Case 3 After six weeks, the dense tube is surrounded by a lighter oval area

senses and to such vagaries as "personality" and "intuition"

My conclusions are illustrated by the following cases

1 Diaphragmatic eventration This patient had been diagnosed as a neurotic His history and behavior strongly suggested this, but the roentgen rays revealed his true condition

2 Chronic nephritis without hypertension, cardiac hypertrophy, or retinal changes This was an atypical case in which all the cardinal clinical symptoms of chronic nephritis were absent On the contrary, the symptoms were so strongly indicative of gastric ulcer that for six months this

patient was treated for this condition by a competent gastroenterologist Without the chemical study of the blood, the diagnosis was almost impossible

3 Unusual case of cholelithiasis This was correctly diagnosed by the history and physical examination, but was confused by the improper use of the roentgen rays Had a plain plate of the abdomen been taken before administration of the barium, this error might have been avoided This case, then, illustrates the value of the older clinical methods as well as the importance of using the newer methods properly

REFERENCES

- ¹DARWIN, CHARLES The descent of man and selection in relation to sex, ed 2, New York, D Appleton & Co, 1899, p 34
- ²Ibid, p 32
- ³ASSMAN, HERBERT Die klinische Röntgendiagnostik der inneren Erkrankungen, ed 4, Leipzig, F C W Vogel, 1928, p 438
- ⁴HIRSCH, CARL Zur klinischen Diagnose der Zwerchfellhernie, München med Wchnschr, 1900, xlvii, 996-999
- ⁵LEICHTENSTERN Zur Diagnose der Hernia diaphragmatica, Berl klin Wchnschr, 1874, xi, 497-500, 515-517, 539-542
- ⁶CARMAN, RUSSEL D, and FINEMAN, SOLOMON The roentgenologic diagnosis of diaphragmatic hernia with a report of seventeen cases, Radiology, 1924, iii, 26-45
- ⁷SORESI, ANGELO L Diaphragmatic hernia its unsuspected frequency its diagnosis technic for radical cure, Ann Surg, 1919, lxi, 254-270
- ⁸FUNK, ELMER H The diaphragm, anatomic and physiologic considerations, methods of examination, conditions associated with altered positions of the diaphragm, diaphragmitis, Med Clin N Am, 1921, iv, 1045-1082
- ⁹FUNK, ELMER H, and MANGES, W F Eventration of the diaphragm with report of a case, Am Jr Med Sci, 1921, clxii, 348-352
- ¹⁰WALTON, HENRY J Eventration of the diaphragm, Am Jr Roentgenol, 1924, xi, 420-426
- ¹¹HITZENBERGER, KARL Das Zwerchfell, Wien, J Springer, 1927, p 152
- ¹²PEPPER, PERRY O H Diseases of the thorax and its viscera, including the heart, lungs and its blood vessels, Progr Med, 1920, iii, 17-136
- ¹³STIVELMAN, B P False pneumothorax, Jr Am Med Assoc, 1920, lxxiv, 12-14
- ¹⁴CLOPTON, MALVERN B Eventration of the diaphragm, Ann Surg, 1923, lxxviii, 154-163
- ¹⁵ALLAN, W A case of eventration of the diaphragm, Virginia Med Month, 1920-1, xlvii, 305-307
- ¹⁶BANNICK, EDWIN G Severe chronic glomerular nephritis without hypertension, cardiac hypertrophy, or retinal changes report of two cases, Arch Int Med, 1927, xxxix, 741-747
- ¹⁷BENNETT, IZOD T Nephritis, its problems and treatment, Oxford University Press, 1929, p 26
- ¹⁸FISHBERG, ARTHUR M Hypertension and nephritis, Philadelphia, Lea & Febiger, 1930, p 370

Auriculoventricular Nodal Rhythm*†

With Report of Cases

By CARL V. VISCHER, M.D., F.A.C.P., and LOWELL L. LANE, A.B., M.D.,
Philadelphia, Pa.

EXPERIMENT has demonstrated that not only the sinus node but the A-V node, the auriculoventricular bundle of His and the bundle branches, with their arborizations have the capacity for impulse production. This fact was established by the Stanis' ligatures. If a ligature is tied around the sinus of a frog's heart, or placed below the level at which the cardiac rhythm is generated, the heart ceases to beat temporarily below the level of this ligature, but after a brief standstill takes up a regular rhythm of its own. This new rhythm is generated in a lower center and is slower in rate than the original sinus rhythm. Likewise if a ligature is placed at the auriculoventricular border a short pause in the contractions is followed by the initiation of a new rhythm which has its origin in the ventricle (idioventricular rhythm), and is still more retarded in rate. These experiments demonstrate that the lower centers have the capacity for impulse production and that the lower the origin of the impulse in the Purkinje system the slower is the rate of impulse generation. In other words

the rôle of pacemaker normally held by the sinus node may, under certain circumstances, be usurped by one of the lower centers.

The center producing the fastest rhythm always controls the heart. As long as the sinus node remains the center of most rapid impulse generation it retains the rôle of pacemaker. The lower centers may gain control over the heart under one of three conditions: in case of depression of sinus rhythmicity, interruption in conduction, or increased excitability of a lower heterotopic center. As long as the sinus node retains its normal rhythm the rapidity of the impulse formation destroys the stimulus to impulse production in the lower heterotopic centers, thus preventing their functioning.

Depression of the sinoauricular node usually results in the automatic transference of the function of impulse production to the auriculoventricular node. This is the phenomenon of nodal rhythm. Experimentally such a condition may be produced by a number of different procedures. Destruction of the S-A node or obliteration of its blood supply will result in the establishment of a nodal rhythm. Cooling of the S-A node will produce the same result. Increased excitability of the

*From the Department of Medicine, Hahnemann Medical College and Hospital, Philadelphia, Pa.

†Received for publication June 1, 1931.

A-V node, caused by a warming of this structure, precipitates a similar transference of the pacemaker. Lewis has demonstrated that nodal rhythm may also follow interference with the nerves of the heart, especially combined stimulus of the right vagus and left sympathetic nerves.

It is now generally accepted that the A-V node is responsible for certain rhythms, characterized by simultaneous contraction of auricle and ventricle. Proof that such a rhythm has its origin in the A-V node was shown by the following experiment. If, during auriculoventricular rhythm, the septum is cooled on the ventricular side of the node, or as Meakins has demonstrated if the bundle is clamped, the ventricle fails in its responses, while the auricle continues to contract. Probably the most convincing evidence that the new rhythm arises in the A-V node is that the rhythm is retarded by cooling and accelerated by heating the region of the node.

Experiments by Lewis have shown that the right vagus has a greater retarding influence upon the sinus rhythm than has the left. The influence of both vagi on rhythm production in the A-V node is powerful. The left sympathetic nerve seems to accelerate rhythm production in the A-V node markedly and to a greater extent than the right nerve, as shown by the fact that isolated stimulation of this nerve may suffice to induce an A-V rhythm.

Clinically the action of the vagus is probably responsible for the depression of the S-A node. The A-V node is then allowed to escape. An escaped beat is a contraction resulting from a

stimulus from a lower center and occurs when there is a long pause in the sinus rhythm as in expiration, blocked auricular extrasystole, sinoauricular block, compensatory pause in ventricular extrasystole or partial heart block. An escaped beat differs from an extrasystole in that the former occurs late in the sinus interval, while the latter is a premature contraction. The incidence of an escaped beat is not infrequently noted, but a true nodal rhythm is relatively rare. Auriculoventricular rhythm may be considered an escape phenomenon and is actually a series of escaped beats.

A temporary nodal rhythm may occur during the vagal slowing of the heart on expiration. Atropine, through its effect on the vagus, will usually abolish an auriculoventricular rhythm, although in some cases this result is not obtained. The same drug may initiate a nodal rhythm. This effect is attributed to a primary stimulating effect on the vagus. An increased excitability of the A-V node may account for the failure of atropine to abolish nodal rhythm in some cases. It has been demonstrated both experimentally and clinically that the vagus is capable of controlling the rhythm produced in the A-V node. Stimulation of the sympathetic by exercise may abolish such a heterotopic rhythm.

Electrocardiographic tracings in instances of nodal rhythm exhibit several characteristic features. The initial and final deflections of each individual complex show the same features as are noted in the nodal type of extrasystole: first, a negative or inverted P wave due to retrograde conduction in the auricle, and second, a shortened P-R

interval Rarely an upright P wave is encountered, which is explained either as a mechanical stimulation of the auricles by ventricular contraction if the P wave follows the QRS complex, or by a variety of intraauricular block with deviated conduction in the auricle The ventricular complex is of the normal supraventricular type The P wave may precede the QRS complex, become buried in it, or follow it, depending on the origin of the stimuli, whether it be in the upper, middle or lower portion of the A-V node (figure 1) The last type in which the stimuli, for contraction, arise in the lower zone of the node is the one most commonly noted in the graphic tracings In such an instance the ventricular contraction precedes the auricular beat, thus giving rise to an R-P interval in place of the normal P-R interval of sinus rhythm A résumé of two cases observed within the past year is here presented

Case I A man, aged 46 years, admitted to the medical ward with the complaints of dyspnea and of cough No information of clinical importance could be obtained from his past history He first noticed shortness of breath two years previously This had increased progressively, and was accompanied by a cough productive of blood-streaked, watery sputum several days previous to admission Examination revealed a cardiac enlargement to the left, a poor cardiac muscle tone, and a mitral systolic murmur The pulse was regular in rhythm, rate 52, and the blood pressure 210/130 There was evidence of congestion at both lung bases A Wassermann test taken the day after admission was negative The patient failed to respond to appropriate medication, dyspnea increased, pulmonary edema supervened, a progressive fall in the systolic blood pressure was noted, and he died three days later of cardiac failure

It is interesting to note that the pulse rate remained between fifty and sixty until

the time of death, despite the failing cardiac function This clinical factor was suggestive of heart block An electrocardiogram taken two days before death revealed an auriculo-ventricular nodal rhythm with the characteristics previously described (figure 2)

Case II A woman, aged 43 years, had been troubled with palpitation and dyspnea, with occasional precordial pain on exertion for a period of several weeks Three years previously she had received treatment over a period of eight months for an active luetic infection, resulting in a negative Wassermann reaction The patient stated that she was quite well until the onset of the above features in February of the current year Clinical examination showed evidence of cardiac enlargement to the left, by physical signs and fluoroscopy, an apical systolic murmur and an accentuated high-pitched aortic second sound The pulse was regular, rate 50, and the blood pressure 130/80 There was no evidence of congestive heart failure A diagnosis of cardiovascular syphilis seemed justified Electrocardiographic tracing made at this time showed the presence of an A-V nodal rhythm (figure 3)

This patient received 1/25 gram of atropine sulphate hypodermatically to note its effect on the cardiac rhythm A tracing taken fifteen minutes after injection showed a persistence of the nodal rhythm, with some increase in rate (figure 4) This result may be explained either as a primary stimulating effect on the vagus, or an enhanced activity of the A-V node Six days later, with the return of sinus rhythm (figure 5), it is interesting to note that the patient experienced marked improvement in her symptoms of dyspnea and precordial distress

The phenomenon of auriculoventricular nodal rhythm is a rather rare clinical finding In a survey of the last 1800 tracings taken in the Electrocardiographic Department of Hahnemann Hospital only four cases were recorded The condition is usually recurrent in character and of short duration It is often noted in alternation with normal rhythm In unusual cases the

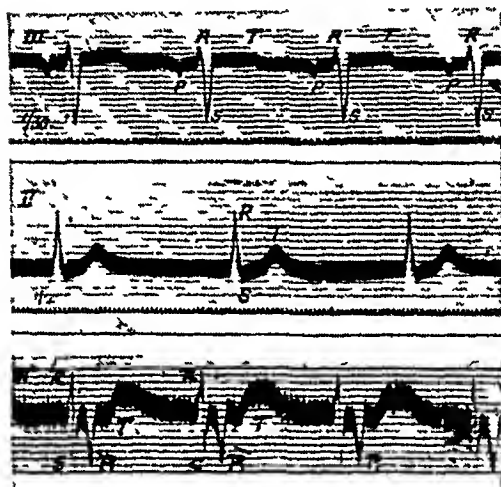


FIG 1 Examples of three types of nodal rhythm. The upper tracing shows inverted P wave preceding the ventricular complex, resulting from impulses originating in the upper portion of the A-V node. In the type exemplified in the middle tracing the impulses arise in the middle portion of the node, causing a simultaneous contraction of auricle and ventricle. The P wave is buried in the QRS complex. Lower tracing shows most common type of A-V rhythm in which the lower portion of the node is site of impulse generation. Inverted P wave follows QRS complex.

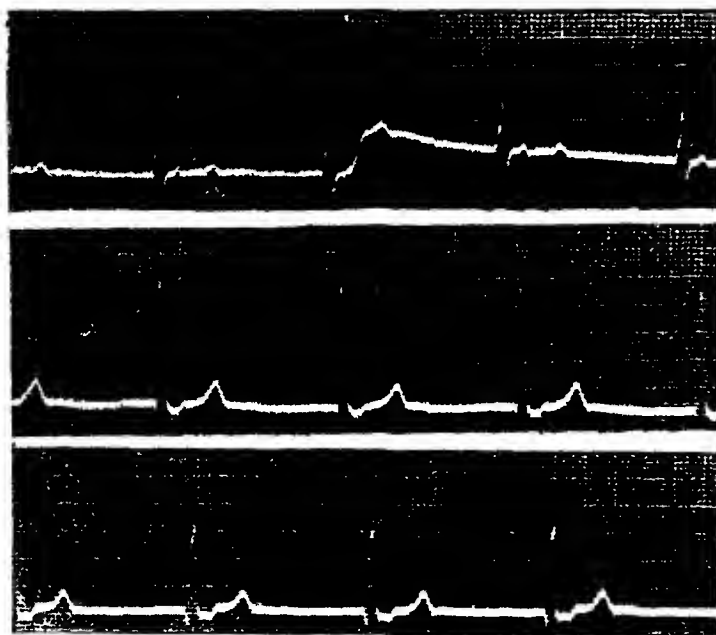


FIG 2 Electrocardiographic tracings of case I, showing A-V rhythm of most common type, with negative P wave, preceded by the ventricular complex.

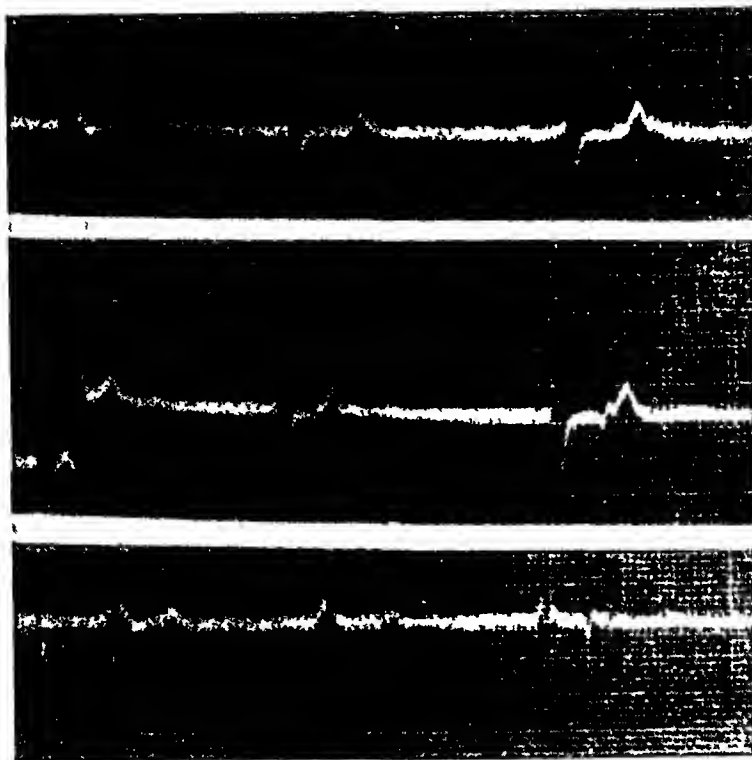


FIG 3 Graphic record of case II An A-V nodal rhythm resulting from impulses originating in lower portion of node

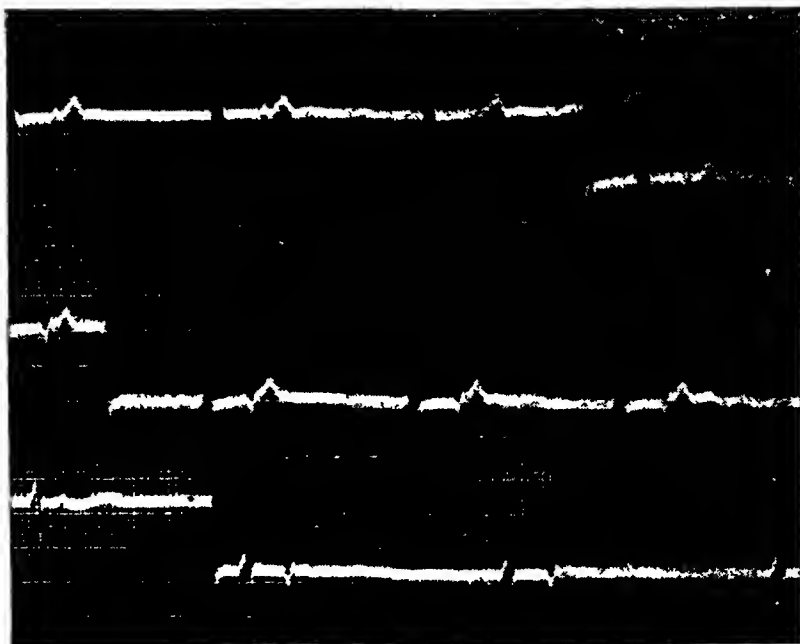


FIG 4 Case II following administration of $\frac{1}{25}$ of a gram of atropine sulphate Note persistence of nodal rhythm with some acceleration in rate of impulse production

A-V node may control the cardiac rhythm for weeks, or even months, at a time. Definite clinical evidence of its presence is usually lacking, except that in cases where the auricle and ventricle contract simultaneously, regurgitation from the right auricle may produce a large wave in the jugular vein. In such instances venous tracings will show a more or less simultaneous occurrence of the A and C waves, producing a large single wave. The heart rate is usually slow, between forty and fifty per minute in most cases, which represents the rate of impulse production in the auriculoventricular node.

Such a heterotopic rhythm may or may not be associated with cardiac disease. The two cases here reported did occur with definite evidence of cardiac

dysfunction. Nodal rhythm, *per se*, is an interesting finding, but is apparently of little or no clinical significance. The importance of the condition is evidenced in the necessity of differentiating it from the vastly more serious entity of heart block suggested by the presence of bradycardia, which is common to both disturbances. A bradycardia of sinus origin must also be considered. Diagnosis must usually be made by the electrocardiogram. Prognosis and treatment in cases of auriculoventricular nodal rhythm are entirely dependent upon the associated cardiac pathology.

The authors desire to express their appreciation to Miss Florence Holstem, technician, for her cooperation in preparing the electrocardiograms used in this paper.

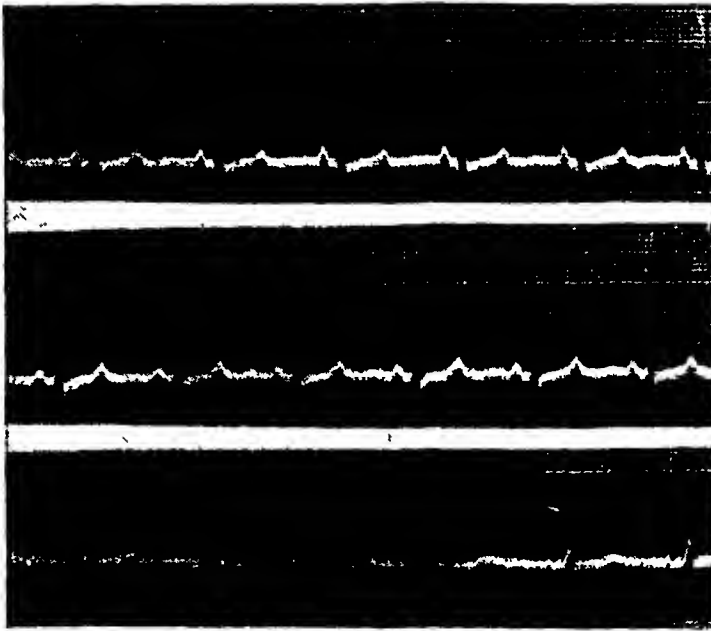


FIG 5 Tracings of case II six days following atropine injection. Return of normal sinus rhythm.

REFERENCES

- | | |
|---|---|
| LEWIS, T The mechanism and graphic registration of the heart beat, 1921, Paul B Hoeber, New York | PARSONNET, A E, and HYMAN, A S Applied electrocardiography, 1929, Macmillan Company, New York |
| LEWIS, T · Clinical electrocardiography, 1928, Shaw and Sons, Ltd, London | WHITE, P D Heart disease, 1931, Macmillan Company, New York |
| EAST, C F T, and BAIN, C W. C · Recent advances in cardiology, 1931, P Blakiston's and Sons, Philadelphia | GÉRAUDEL, É · The mechanism of the heart and its anomalies, 1930, Williams and Wilkins Company, Baltimore |

Creative Evolution and Prosperity

THE theory of "creative evolution" recognizes the fact that the whole may be more than the sum of its parts. A dog is more than an aggregate of carbon, hydrogen, nitrogen, and phosphorus, supplied with certain energy, and its nature never could be discovered by a study of the elements of which it is made. A symphony orchestra is more than an aggregate of individual musicians. Only when each player finds his personal expression in a unity with the entire orchestra and in contributing to the most perfect total effect does a great symphony appear.

American prosperity, through exceptional circumstances, reached a high crest. That climax of prosperity may prove to have been but the rare crest of a wave if those in business see themselves as independent units, each striving primarily for his own satisfaction. For prosperity of a high type to be permanent it will be necessary for individual and corporate interests to be subordinate to the aim of producing a high and generally distributed well-being. Just as a football team cannot greatly succeed if it is made up of star players each bent on distinguishing himself regardless of the game as a whole, so it is with business.

Those familiar with the motives of some "re-financings" and mergings of the recent past, with the selling of great quantities of stock to the public at high prices, as well as other business practices of the period of prosperity, are aware that the subordination of special interests to the general good is not yet a dominant trait of American business.

Permanent prosperity on a high level will evade us until that spirit is dominant. Except as economists take such factors into account, the disappearance of prosperity will continue a mystery. If creative evolution can take place in our economic life, general prosperity can increase to levels heretofore unknown. It will be better if this comes from the spirit of the times, rather than from enforced government action — (A E M, in *Antioch Notes*, Vol 9, No 7, January 15, 1932)

Somatic Disorders of Functional Origin*†

By S KATZENELBOGEN, M D , F A C P , *Baltimore, Md*

SOMATIC disorders of functional origin present quite a common problem in general medicine as well as in any of its special branches. In dealing with this subject one question immediately arises: Is it possible, or is one altogether justified in drawing a hard-and-fast line between "functional," so-called, and "organic"? Those "organicists" who believe in such a clean-cut demarcation, who are trained to think in terms of lesions exclusively, and to whom therefore complaints and even objective disorders have a meaning only when they can be reasonably explained by a detectable organic alteration, would do well to remember the following facts. In the domain of Neurology, the last three decades have witnessed an extension of the group of organic diseases of the cerebrospinal nervous system at the expense of the group of functional diseases. I allude to such diseases as chorea, athetosis, Parkinson's disease, and Thompson's disease, which have been successively transferred from the functional into the organic group. This fact may be grati-

fying to the organicist, but it should also serve as a warning against a loose attitude towards functional disorders, which, for many physicians, under the label of "neuropathy," are quite equivalent to "imaginary malady." I should also like to call your attention to some facts in other domains. Clinical and anatomo-pathological observations have brought to light the concept that the morbid manifestations of such an organic disease *par excellence* as angina pectoris appear to be controlled by a functional factor. Such a belief has its basis in the fact that one finds on post-mortem examination sclerosis of the coronary artery in persons who never had *anginal attacks*. Moreover, in certain patients who did suffer from typical attacks of angina pectoris, and displayed evidences of a marked excitability of the vegetative system, the anatomical examination did not reveal lesions in the myocardial vessels, nor could any lesion of the vegetative system be discovered. It has also been found that the occurrence and frequency of attacks in such organic diseases as symptomatic asthma and biliary lithiasis are more or less conditioned by the functional state of the autonomic nervous system. These observations sufficiently demonstrate the fragility of the lines drawn between organic and functional. Besides, the

*Presented at the Fifteenth Annual Clinical Session of The American College of Physicians, March 25th, 1931, Baltimore, Md.

†From The Henry Phipps Psychiatric Clinic (Department of Internal Medicine) Johns Hopkins Hospital, Baltimore, Md.

usual opposition of "functional" versus "organic" does not seem to rest upon a sound basis, for the so-called functional disorders are associated with definite changes in secretion and motility of organs, they are accompanied by alteration of the physicochemical status of the blood and other bodily fluids. These modifications present organic disorders going hand in hand with the altered function, and, needless to say, are capable of causing as much distress as structural disorders. It would therefore seem more appropriate to use the term physiogenic as applied to both "organic" and "functional" disturbances, bearing in mind that in organic disorders the altered function is accompanied by histological changes and in purely physiogenic disorders, only physicochemical changes may be found. As to the "psychogenic bodily disorders" they are obviously also attended by altered physiological functions. The term psychogenic only implies the notion that certain psychological factors take part in the causation of the physical disorders. Functional hyperchlorhydria, for instance, may be induced by certain physical stimulants, highly seasoned food, alcohol, or by affective disorders, in which case it will be of psychogenic origin.

In this necessarily sketchy presentation, I should like to bring to your notice some of the commonest functional disorders. Pain is one of these troubles and it calls for special attention not only on account of its distressing, incapacitating effect, but also because this is a warning that something is wrong. Excluding from the discussion pain associated with detectable physical disease, one may ask whether purely psychic factors are able to induce pain in

apparently normal individuals? In answering this question I refer to the following two cases, which, in my judgment, illustrate psychogenic pain.

I. A man, 43 years old, graduate chemist, had suffered from a severe attack of sciatica for over a year. The recovery was complete and no relapse had taken place during the six years he was known to me. He presented, however, the following curious phenomenon. On many occasions when reminded of his previous illness, or when he was thinking about the possibility of a recurrent attack, he experienced severe, but fortunately very transitory pain in his leg, without developing, otherwise, neurasthenic or hysterical features.

In the second case, suggestion of a very protracted character was evidently the cause of the evil.

A young man, a medical student, had been suffering from dull pains in the back of the head. The history revealed that the trouble started after he had been painfully impressed by the death of a classmate from cerebral tumor. Notwithstanding the fact that his fear of also having a tumor was dissipated by the entirely negative physical examination, his head sensations, more or less pronounced, had persisted during the four years I knew him.

Psychogenic pain may also be exemplified by the following two cases observed in this clinic.

A woman, among other troubles, complained of soreness of the tongue. This complaint became particularly prominent and persistent after a suspicious diagnosis of cancer, based on some enlargement of the papilla on the base of the tongue, was made. The patient continued complaining of pain long after the local symptoms had subsided.

Another patient came to this clinic because of attacks of soreness of the tongue which had taken place on several occasions during her lessons in school and for which talking was blamed. I must add that there was a certain physical background in the beginning, namely, throat and sinus troubles which may raise the question of referred

pain But during her stay here, in spite of the fact that she still had remnants of her previous condition in the throat and antrum and was very talkative, she did not have any pain It therefore seems plausible to assume that we are confronted here with pain of recollection analogous to the case of sciatica which I have just recorded The fear of losing her position should attacks of pain which she originally experienced while teaching recur, made her on certain occasions think vividly of this experience during her lessons and feel accordingly

As to the mechanism of psychogenic pain, the following conjectures may be considered 1 Psychic stimulation with response of certain areas of the brain, such as the thalamic region, center of pain sensations, from which pain is projected to the periphery, as it is assumed to be in organic central pain 2 Pain is known to be frequently associated with vasomotor disorders regarded by some writers, not without plausible reason, as the immediate cause of pain, be it of central or peripheral origin The last mentioned hypothesis seems the more plausible because pain is a common complaint of psychoneurotic individuals who, besides, usually display evident vasomotor disturbances.

Another complaint not substantiated by somatic findings is fatigue It may have but little bearing on the muscular strength or muscular tone It will be found that this type of fatigue is rather closely related to lack of interest in the particular effort which causes it, and may therefore be termed selective fatigue Being functional this kind of fatigue is, however, not infrequently associated with loss of weight, as a result of loss of appetite, and inadequate food intake

Functional cardiac troubles constitute perhaps the most conspicuous

chapter in functional pathology Their symptomatology shares, with that of functional disorders of other vital systems, the common character of being mainly subjective Sensation of pressure, pain in the cardiac region, sometimes with radiation to the left arm, palpitations, inability to take a deep breath are common complaints The latter, usually of a rich variety are, however, not referred to the heart only The objective examination will reveal symptoms with which we are all familiar, such as tachycardia of the transitory type, hyperkinesis, extrasystoles, systolic murmurs usually localized in the mesosternum, and vasomotor lability Here I should like to call attention to a special type of cardiac neurosis That is the syndrome known in the literature of war neurosis as "irritable heart of the soldier", or more commonly in the general medical literature as "effort syndrome", or "neuro-circulatory asthenia" As the last named term suggests, the troubles are referred to both the circulatory and nervous systems

In addition to complaints and objective symptoms common in functional heart disorders, there are other features which dominate the clinical picture Fatigue, usually more pronounced in the earlier part of the day, dizziness, giddiness particularly liable to occur when the sitting position is changed to a standing one, general shakiness, fainting, with or without complete loss of consciousness, excessive susceptibility to cold, sleeplessness, inability to fix the attention, and lack of interest This syndrome may be found in juvenile cases, and in adults, and is not infrequently responsible for the accusation of "laziness" among school boys

and girls. In many cases a constitutional origin is suggestive. In others, this syndrome appears to be a sequel of a toxic-infectious condition. In the last named cases one will be confronted not infrequently with the dilemma as to whether the protracted effect of the toxic-infectious condition is solely to be blamed, or whether the oversolicitous family or doctor are not partly responsible for keeping the patient away from his duties longer than is absolutely necessary, with the consequent worries about waste of time and loss of the patient's selfconfidence.

Finally, I want to call attention to some of the functional gastrointestinal disorders. Numerous experimental investigations and clinical observations of patients with gastric fistula, observations having the value of experiments, are available, which point to certain etiologic factors of the so-called nervous indigestion. These studies demonstrate that affective imbalance, and mainly acute emotion (anger, anxiety, fear, etc.) strongly influence the gastric secretion. The latter usually increases under pleasant emotions (sight or smell of food, pleasant environment while eating) and decreases under unpleasant ones. This relationship between secretions of the digestive system, and emotions is an old notion familiar even to laymen, as indicated by the ancient test used in India to pick out a thief from a group of suspicious persons, a test in which each person is given a bowl of rice and the criminal is detected by his dry mouth, and inability to insalivate the rice.

The motor function of the alimentary canal may be equally controlled by psychic factors. Here again I refer to the common observation of physiolo-

gists, demonstrating that uneasiness, discomfort, and anger, experienced by animals, immediately induce cessation of the gastrointestinal movements. If under these conditions the splanchnic nerves are cut, the inhibition will be reduced to a great extent. On the other hand, clinical and radiological investigations on men, also demonstrate the inhibitory or stimulating effect of emotion on the gastrointestinal motility. The barium meal may remain in the stomach for many hours without moving, in individuals under nervous strain in whom no organic alteration is recognizable. Psychic stimulation may also have the opposite effect, namely, to increase the motility. In this respect the following case may be illustrative.

A man who, in his capacity of a high official in an international institution, had to attend banquets and various social gatherings, suffered from the following trouble. On many of these occasions, as soon as he started eating he had to leave the table, summoned by the call of nature. No organic cause for this trouble could be detected. On the contrary, the history of the disease was very illuminating. This man had been brought from obscurity into prominence during a revolution in his country. From a modest social standing, an humble member of the socialistic party, he suddenly found himself a representative of his country in the institution of highly trained diplomats. This turning point which threw him into a *milieu* and conditions not usual to him, was the beginning of his troubles, obviously on an emotional basis.

Finally, radiological examinations showing the reverse current in the digestive tract in certain patients, while under emotional strain, substantiate the clinical observations of vomiting in neurotic individuals, in whom no causes other than effective disturbances can be revealed.

The problem of etiology, pathogenesis of functional disorders in general, and of the gastrointestinal disorders in particular has given rise to theories implicating the autonomic nervous system. These theories advocating the conception of sympathicotonia and vagotonia, that is, of an imbalance between the two antagonistic parts of the visceral nervous system, had a wide vogue after they were propounded by Eppinger and Hess in 1910. Now, we should all be familiar with the fact that the subdivision of neurotic individuals into two clean-cut reaction types is not warranted by clinical observation. It is true that in certain subjects there are evidences suggestive of a certain predominance of one set of the vegetative nerves—the sympathetic or the parasympathetic. But what we commonly meet with in neurotic individuals is a disturbed function involving both portions of the visceral nervous system. One usually observes a dystony which may manifest itself not only by a relative increase of the controlling power of one portion, but also by an increase or a lowering of the tone of the whole visceral nervous apparatus.

From the etiologic standpoint the malfunction of the autonomic nervous system raises the question of the rôle of constitution, the rôle of toxic-infectious conditions and other physical factors. Another element weighing heavily in disorders of the viscera under the control of the vegetative system, an element which is commonly not given adequate consideration by the physician at large, by the internist, and general practitioner, is the emotional one. Of course, the relationship of cause and effect is open to debate. One may ask whether the excessive responsiveness

of the visceral organs to certain life situations is conditioned by inherent or acquired malfunction of the autonomic nervous system or of the viscera themselves under its control, or are these excessive reactions only a proportionate response to strong emotion proper to the psychobiological endowment of the individual involved? Leaving this question out of the discussion it suffices for our purpose to note the fact that affective imbalance, arising from life conflicts and not infrequently from pleasant life experiences also, is attended by more or less pronounced reactions of the vegetative organs. Moreover, it is well to bear in mind the notion ably advocated by Cannon, that affective disorders, when they repeat themselves, are able to sensitize the vegetative system which will then react excessively, even to a mild emotional upset.

In concluding I would like to emphasize the three following points:

1. The so-called functional disorders are not "imaginary maladies," and they may cause as much discomfort and distress as organic structural diseases.

2. Functional disturbances may be induced by various factors, physical as well as psychological.

3. A thorough physical examination should therefore be supplemented by a no less thorough inquiry into the conditions within and without under which the troubles originated and developed. Such an investigation is obviously imperative whenever no somatic basis for bodily disorders can be found. Moreover, one should be attentive to the fact that manifestations of organic-structural diseases may also be greatly influenced by psychological factors.

Advanced Pulmonary Tuberculosis*

By LEWIS J. MOORMAN, M D , F A C P ,† *Oklahoma City, Oklahoma*

FOR many decades the dominant theme of practically all discussions dealing with clinical tuberculosis has been early diagnosis and early treatment. While the significance of this theme is perfectly obvious and the difficulty of early diagnosis universally admitted, there still seems to be a general lack of interest in tuberculosis. This may be accounted for in part by the fact that, until recently, we have been unable to offer any constructive variation in a program which often proved inadequate. It is not surprising that many members of the profession not particularly intrigued by the interesting game of physical diagnosis, and not committed to the rather difficult task of phthisiotherapy, should manifest a certain amount of indifference.

Without intensive study there can be little first hand knowledge of the fascinating course of this versatile disease with its ever changing interplay of virulence and resistance, there can be no adequate appreciation of the fact that the relative dominance of these two factors, determines the clinical

course and the pathological variants which range from those manifested through the racing catastrophe of florid phthisis to the relative security of insidious fibrosis. Since tuberculosis continues to be one of the prime factors in morbidity and is responsible for one-seventh of the world's mortality, it deserves the serious interest of the medical profession.

While it is necessary to maintain our emphasis upon early diagnosis and early treatment, it is most gratifying to be able to recount the fact that recent advances in the treatment of pulmonary tuberculosis offer a new hope to those suffering from the more advanced conditions which might otherwise be considered hopeless. Considering the three cases which Dr. Pincoffs has so kindly provided for this clinic, I am indeed pleased to say that our present therapeutic measures are sufficiently flexible to meet many of the wide variations in pulmonary pathology. Many of these variations are exhibited in the cases now to be presented and in addition to the established routine, rest, dietetic and hygienic management, they call for a discussion of the following therapeutic method: artificial pneumothorax, the curettage of pleural adhesions, the various operations on the phrenic nerve and the use of the

*Presented at the University of Oklahoma School of Medicine, University Hospital, the University Medical Clinic and the Oklahoma State Tuberculosis Hospital, Oklahoma City, Oklahoma, June 1934.

CASE I

The first case, C B, is a young colored woman thirty-three years of age, married, no children, but in contact with two children in the home where she is employed to do general housework. Family history negative, except contact with a luetic husband. No history of known contact with tuberculosis. Past history otherwise negative except the loss of about sixty pounds during the past year.

Present Illness In the early part of December, 1930, while at her usual work, she developed a headache, soreness in the chest and weakness. These symptoms were promptly followed by a chill and high fever. A cough and hoarseness developed. After two days she returned to work. Her cough continued and a few weeks later it became productive with a gradual increase in sputum. Three weeks ago, March 3, she had to quit work on account of increasing weakness. She was examined in the outpatient department one week ago and was admitted to the Hospital with a diagnosis of bronchopneumonia, possibly tuberculous in character. Since admission she has shown a temperature range of 99 to 102, pulse 80 to 105, respiration 20 to 30. She has continued to cough and the record indicates that she has raised four ounces of sputum daily.

Physical examination shows limited respiratory excursion on the right, palpation is negative, percussion elicits dullness from the third rib anteriorly to the base. This dullness extends well into the axilla but there is very little impairment posteriorly. The left shows no demonstrable impairment of resonance. Auscultation reveals numerous fine and medium râles over the lower half of the right chest with large bubbling and occasional musical râles on a level with the fourth right interspace anteriorly. These râles are suggestive of the presence of cavity, though there are no other signs to aid in the diagnosis of cavity. With the exception of a few crackling râles along the left border of the heart, auscultation on the left is negative.

An examination of the sputum showed many tubercle bacilli, the blood and urine were reported negative. Blood Wassermann

test was found to be four plus. A flat film of the chest made upon admission shows marked opacity in the lower half of the right lung, suggesting widespread infiltration of varying density. Extending from the lower angle of the right hilum there is an oval density with a rarified center, suggesting a cavity. Stereoscopic films made yesterday present unmistakable evidence of a cavity about five by eight centimeters in diameter. In the parenchyma of the right lung opposite the fourth rib, there is a small calcified node. This, associated with calcification about the hilum, suggests a childhood infection. The left hilum is heavier than normal and there is a generalized fibrosis with a little patchy infiltration in the lower half of the lung (Figure 1).

The diagnosis in this case is pulmonary tuberculosis with rapid caseation and liquefaction with cavity formation. There is evidently an acute bronchogenic spread into the lower right, giving rise to a tuberculous bronchopneumonia. The defensive reaction seems to be wholly inadequate, there is practically no evidence of fibrosis and the course of the disease would suggest that not only has there been a failure on the part of the defensive forces to react with the formation of fibrous tissue, but even the reticulum fibers have gone down under the virulent onslaught allowing the disease to progress rapidly.

However, the patient has shown a progressive gain in general physical well being since admission to the hospital which is encouraging. In spite of the apparently acute course of this case the prognosis is not utterly hopeless. The right diaphragm exhibits a fairly free excursion and it is possible that the pleural space is free. If collapse can be obtained by means of artificial pneumothorax the cavity may

be closed and the progress of the disease arrested

I should advise this course regardless of the slight present trouble on the left side. If the overwhelming load of toxemia can be even partially lifted by pneumothorax on the right we may expect recession rather than progression of the disease in the contralateral lung. If adhesions should be encountered and if they should happen to be of such a character as to justify the Jacobaeus operation (thoracoscopic visualization and cauterization) the handicap of limited collapse might be overcome. If this should prove impractical, phrenicectomy might be indicated. If one or all of these methods should result in marked improvement and yet prove insufficient to close the cavity, cautious employment of thoracoplasty might be considered. If the contra-

lateral lung should happen to take on a progressive phase under such procedures, partial collapse of the left lung by means of artificial pneumothorax might be undertaken, even though it should necessitate simultaneous bilateral pneumothorax. Such a case is not to be considered favorable for any type of treatment, yet the hopelessness of the case if untreated seems to warrant a trial, especially as the results in such cases are occasionally surprisingly good. The presence of an active luetic infection may exert an unfavorable influence through lowered resistance. Antiluetic treatment should be guarded because of the acute character of the tuberculosis.

CASE II

The next case, A W, is a man forty-two years of age. Family and personal history uneventful except contact with father who coughed and expectorated over a period of



FIG. 1. Case I. Advanced pulmonary tuberculosis predominating at the right base. Large cavity at the right border of the heart extending between third and fifth ribs.

many years. While there may be some question as to the diagnosis in the father's case, this cough was attributed to tuberculosis. The hospital record indicates that the onset of this patient's present illness was three months ago, when he became too weak to continue his daily routine. He developed a cough with moderate expectoration, dyspnea and fever. A close investigation with reference to his past reveals the fact that he gives a history of what might be termed a frank pleurisy two years ago and that he has coughed and expectorated for years. As may be seen later, this additional history is in keeping with the physical and pathological findings.

The patient was admitted to the City Hospital two weeks ago. Since this time his temperature has ranged from 98 to 100, his pulse from 72 to 90, respiration from 20 to 30, sputum, four ounces. He has manifested symptomatic improvement with some reduction in sputum. The laboratory reports show that the blood and urine were negative. Sputum showed many tubercle bacilli. Physical examination at the present time reveals a well developed man showing no particular evidence of loss of weight. Inspection with

reference to the thorax elicits nothing of importance. Palpation is likewise negative except for moderate increase in palpable fremitus at the left apex. Percussion reveals dullness on the right from the fifth rib up, on the left from the first rib up with slight impairment extending as low as the fourth rib. Posteriorly, resonance is impaired on the right from the apex to the lower angle of the scapula, and on the left as low as the fifth vertebra.

The right diaphragm is practically immobile. Auscultation shows that the breath sounds are slightly diminished over the whole right, but exaggerated at the left apex. Fine and medium crackling râles are to be heard over the whole of the right and the upper half of the left. At the left apex coarse bubbling and musical râles are heard. These signs with exaggerated breath sounds are sufficient to warrant a diagnosis of cavity at the left apex. There are no demonstrable signs of cavity on the right side. A flat film of the chest presents unmistakable evidence of old fibrocaseous disease at both apices with definite cavity formation at the left. (Figure 2) Above the level



FIG 2 Case II Advanced bilateral pulmonary tuberculosis with cavity formation

of the first rib on the left, the film suggests an old pleuritis with marked thickening, giving rise to the so-called pleural cap. On the right side there is a generalized patchy infiltration extending as low as the fifth rib anteriorly. There is also a similar area on the left extending from the hilum and fusing with the old pathology at the left apex.

This widespread dissemination of what appears to be recent disease is in all probability a bronchogenic spread of an old infection and we may be justified in assuming that it is contemporary with the recent exacerbation of symptoms. On the right side opposite the first rib there is an illly defined thin-walled cavity about $2\frac{1}{2}$ centimeters in diameter. This evidently is likewise of recent origin. The right costophrenic angle is poorly defined and there is obvious peaking of the right diaphragmatic dome suggesting adhesions, which may be dated back to the pleurisy two years ago and which may be utilized to explain marked limitation of diaphragmatic excursion on the right as shown by percussion. You readily appreciate the fact that we have little to offer in this case, yet the low grade toxemia in the presence of such widespread disease suggests a fighting chance. Leaving out of consideration the economic phase of such a case and assuming the possibility of long continued institutional treatment, the following procedure is suggested. Since the acute manifestations are more extensive on the right with a small cavity, the walls of which are not sufficiently fibrosed to materially resist collapse, I would suggest artificial pneumothorax even though adhesions are certainly present. Partial collapse often accomplishes great good and places the pa-

tient in a condition to withstand more radical procedures. In case pneumothorax is impossible on account of obliterating pleurisy or in case basal adhesions are extensive and cannot be cauterized, the pneumothorax may be supplemented by phrenicectomy. If the results of treatment on the right are promising, circumscribed thoracoplasty might be employed to close the old cavities at the left apex.

CASE III

Wm. Y., age sixty, is married and a cigar maker. Past history is negative until five years ago from which time he dates his present illness. Family history is negative. Five years ago he first noticed symptoms of nasal obstruction which was associated with cough. A few months later he had an operation for the relief of this nasal obstruction and something was removed from his nose. His cough continued with increasing expectoration. Three years ago he suddenly developed an attack of asthma which required a hypodermic before he got relief. Since that time he has had wheezing with irregular periods when he would have frank asthmatic attacks. He was admitted to the City Hospital two months ago. His temperature occasionally reached 100, but it has been normal the past six weeks. Pulse, 100 to 120, respiration, 20 to 25, blood pressure, 112/80. Sputum was sixteen ounces daily at first, now about eight ounces. Cough is worse during the night and is paroxysmal in character.

Examination reveals the classical signs of chronic bronchitis with emphysema. Wheezing and crackling râles throughout both lungs. The examination is otherwise negative except at the left apex where are to be found all the signs of fibrocaceous tuberculosis with cavity formation. The trachea is displaced to the right. The reported laboratory findings, including a blood Wassermann test, are negative. Five sputum examinations failed to show tubercle bacilli. With such large quantities of sputum one would naturally expect to find tubercle bacilli if tuberculosis constitutes the chief source of the sputum. In this case there is a his-

tory of asthmatic attacks with long continued bronchitis. It is reasonable to presume that even though the diagnosis of chronic pulmonary tuberculosis is justified there must be some associated condition to account for much of the sputum. Naturally one would suspect a bronchiectasis.

A flat film of the chest as you may see, reveals typical evidence of chronic fibroid tuberculosis at the apex of the left (Figure 3). Strange to say the mediastinum is displaced toward the right, which accounts for the visible and palpable displacement of the trachea toward the right. The lung fields show a generalized fibrosis with rather marked fibrosis extending from the right hilum to the right apex. This latter probably represents an old healed lesion with scar tissue and adhesions which displaced the trachea and heart toward the right, and fixed them in this abnormal position before the fibrotic pull was exerted on the left. There is evidence of diaphragmatic adhesions on both sides and perhaps a slight suggestion of bronchiectasis at the right base.

My impression in this case is as follows: an old healed tuberculous lesion, upper right; chronic caseofibrous

tuberculosis with cavity formation at the apex of the left, chronic bronchitis with bronchiectasis and emphysema. The nose and throat examination revealed a pansinusitis. In this case the sputum should be examined repeatedly, concentration methods being employed. If persistently negative, cultures should be made or animal inoculation employed. The introduction of lipiodol might determine whether or not he has dilated bronchial tubes and whether the dilatations are unilateral or bilateral. If the bronchiectasis is right unilateral as suspected, or if it predominates on the right side, the right phrenic nerve might be taken. Whether or not anything should be done with reference to the upper left will depend upon the progress of the case. The patient's age and cardiac condition would render any major surgical procedure hazardous. Obviously the sinusitis should have appropriate treatment.



FIG 3 Case III Chronic fibroid tuberculosis of the left apex with a possibility of bronchiectasis at the right base

The Diagnosis of Hyperthyroidism*†

By MAYNARD E HOLMES, M.D, F A C P, *Syracuse, N Y*

THE term hyperthyroidism has been adopted in recent years to designate a symptom complex caused by hyperactivity of the thyroid gland. In the past, patients who are now classified as having hyperthyroidism together with a large group with a similar symptomatology but not of thyroid origin, were diagnosed as having Graves' disease. Kessel¹ has called attention to the latter group and applied to it the term autonomic imbalance, to designate it as a disturbance of the autonomic nervous system.

Moschcowitz² is of the opinion that Graves' disease evolves from a basic neuropathic personality to its full-blown clinical form when hyperthyroidism has secondarily developed. Others have described the Graves' constitution, Basedowoid, pre-Basedow and *formes frustes* as precursors of true Graves' disease. Admittedly only a very small percentage of the large neurogenic group ever develop hyperthyroidism, and prior to the development of an elevated metabolism proof is lacking that the symptom complex is in any way related to the thyroid gland, hence for this group some such terms as autonomic imbalance or

neuro-circulatory asthenia more clearly implicates its neuropathic origin. The real problem in the management of these two groups of patients is not so much that an occasional neurotic individual may develop hyperthyroidism, but from a practical standpoint it is far more important to separate the true thyroid patient from the neuropathic one because they demand radically different treatment. It is perhaps unfortunate that the term Graves' disease has not been restricted to those cases having hyperthyroidism, because the two terms are commonly looked upon as synonymous. The confusion brought about by linking the neurogenic group with the thyroid gland not only leads to unnecessary thyroid surgery, but has in the past, been the cause of considerable dissatisfaction with the treatment of hyperthyroidism, and in like manner no doubt explains the disagreement which surrounds the pathology of thyroid disease.

Until the basal metabolism test was introduced as a clinical procedure in 1920, there was no dependable laboratory method to guide one in the diagnosis of thyroid disease. At present, with the help of this valuable clinical test, it would seem that there should be no valid reason for mistaking a neurosis for hyperthyroidism, and yet the error is still commonly made. Ham-

*From the Department of Metabolism, University Hospital, Syracuse University College of Medicine.

†Received for publication, June 16, 1931.

ilton and Lahey³ report that one-third of the patients referred to their thyroid clinic, after careful study fail to show any disorder attributable to the thyroid gland

Failure to differentiate between the true thyroid syndrome and that of neurogenic origin is in great part due to the fact that many practitioners and particularly surgeons seems to underestimate the part played by functional disorders of the nervous system as a cause of many varied symptom complexes. The surgeon, no doubt because of his daily precise technical problems, develops a frame of mind which does not sufficiently evaluate the part functional disorders may play as a great mimic of organic disease. Medical students formerly were so cautioned against making other than an organic diagnosis that later in practice, they lack the courage to do so. The present day student on the other hand, has fortunately a much more rational understanding of the importance of functional disorders of the nervous system as a great cause of ill health.

The following case reports are given to illustrate the manner in which a simple neurosis is frequently confused with hyperthyroidism.

Case I A woman, aged 42, who had always been nervous and in poor health, complained of vague stomach discomfort and fatigue for five years. Anorexia, constipation, pain in the bowels, headache, lame back, sensitiveness to cold, insomnia and palpitation had been present for two years. She had had two Caesarean operations and her appendix had been removed for chronic appendicitis. She had been told by a surgeon that her symptoms were due to thyroid disease, and thyroidectomy urged. To confirm this opinion she consulted an internist

who found a normal pulse, no enlargement of the thyroid and no evidence of thyroid toxicity. The basal metabolic rate was found to be +8. She had always worked hard, and there had always been considerable domestic and financial worries which no doubt were factors producing her symptoms.

Case II A woman, aged 29, was admitted to the hospital with a diagnosis of hyperthyroidism with surgery recommended. Some enlargement of the thyroid had been present since 14 years of age. Nervousness, fatigue, attacks of nausea and vomiting, headache, backache, anorexia, sensitiveness to cold, palpitation, tremor and emotionalism had been present for eight years, or since marriage. There was a marked nervous tendency in her family, one brother having mental disease. The basal metabolic rate was found to be +1. Since marriage there had been considerable family and financial worries. A neurogenic cause for her symptoms seemed quite evident. Several months later after appropriate treatment for her neurosis, she was found to be almost completely relieved of her symptoms.

Case III A woman, aged 34, who was always of a nervous temperament, developed, after considerable marital trouble, increase in nervousness, palpitation, hysterical seizures and fits of depression. There was no loss of weight, thyroid enlargement or sensitiveness to heat. The metabolic rate was -7. A surgeon was inclined to a diagnosis of hyperthyroidism but finally bowed to the opinion of an internist and neurologist that the patient was suffering from a psychoneurosis. The patient seemed obsessed with the idea that her thyroid must be removed and consulted a surgeon in another city. On the basis of a positive Goetsch test, he performed a thyroidectomy. As might be expected from the normal basal metabolism there was no relief of symptoms and within a year the patient was in an institution for treatment of her mental state.

The value of the basal metabolic test in differentiating the thyroid from the nonthyroid patient is often vitiated because of errors of technic or interpretation. When the test was introduced,

Benedict⁴, DuBois⁵ and others cautioned that the procedure could be of little or no value unless performed by one familiar with all the details involved, and using only the most accurate methods. Certain manufacturers have simplified the apparatus and the compilation of the results to such a degree that it is very easy for considerable error to occur. While there can be little doubt that a well trained technician can accurately perform this valuable clinical test, it is quite another thing to have it performed as it commonly is by one who has had no training except perhaps from a circular or a salesman. The performance of this test which carries so much weight in diagnosis should be as carefully guarded as, for example, the Wassermann test.

Perhaps the greatest error in the interpretation of the results of the basal metabolic test is the significance attached to figures reported only slightly above the limits of normal. It is a common observation to obtain at an initial test figures of from +15 to +35 which at a second or third rate-taking will be found well within the limits of normal. Obviously in such instances the earlier figures do not represent basal conditions and are usually caused by failure of the patient to completely relax. It is most important in the performance of this test that the patients be under basal conditions, otherwise the results are of no value. The candidates for this test are often nervous and apprehensive and hence at times are with difficulty at the first test brought under basal conditions. Ziegler and Levine⁶, Landis⁷, and Henry⁸ have demonstrated that mental un-

rest during the procedure can cause an elevated metabolism as high as +40. To overcome the various possibilities of error and to avoid accepting the results of a single test as confirmation of a diagnosis of thyroid toxicity, a safe rule to follow when the reported findings are elevated is to repeat the test until normal figures are obtained or until the rate reaches a stationary level. Figures reported up to +15 should be considered within the limits of normal especially in ambulatory patients⁹.

The following case histories illustrate the manner in which repeated metabolic studies will finally clear up the diagnosis.

Case IV A woman, aged 58, had suffered from pains in her legs for several months. A moderately severe grade of diabetes was present, requiring insulin. For some time there had been rather marked nervous and mental symptoms. Feeling that a thyroid adenoma might be the cause of her symptoms, a metabolic test was made. The rate was found to be +26, three days later +24, and on the next day +4. After eighteen months of insulin treatment the patient was found to be greatly improved in health, particularly in respect to the nervous and mental symptoms.

Case V A woman, aged 30, had complained of nervousness and rapid heart action for several weeks. There was no loss of weight, sensitiveness to heat or thyroid enlargement. An internist, feeling that a diagnosis of hyperthyroidism should be considered, ordered a metabolic study. The rate on December 14 was found to be +27, and one week later, +27. She was then admitted to the hospital for further study. Here the metabolic rate was found to be, on January 9, +37, on January 10, +26, and on January 17, +13, which is within the limits of normal. She was discharged somewhat improved with a diagnosis of a neurosis. A rate taken 6 months later gave a figure of +3, all symptoms were relieved.

and there had been a gain of 15 pounds in weight. It would have been very easy to have made the error of removing the thyroid here if repeated metabolic tests had not been made.

Case VI A nurse, aged 21, with previously good health, after taking over the responsibilities of a ward supervisor, developed fatigue, nervousness, rapid heart action, anorexia and some loss of weight. The possibility of the presence of hyperthyroidism was considered. The metabolic rate on May 3 was found to be +26, on May 8, +34, and after a brief rest from her duties the rate was found to be +11. Because of the presence of some nervous and gastric symptoms her vacation was extended for two months, after which she was feeling in the best of health and her weight had increased by 20 pounds. At this time the metabolic rate was found to be +8. Two years have now elapsed with no return of symptoms. Here again repeated metabolism tests cleared up the diagnosis and saved the patient from unnecessary surgery.

The question often arises whether or not hyperthyroidism is ever present when the metabolic rate is normal. The majority opinion, especially of those having extensive experience with the test, is that this is uncommon—perhaps even less common than the presence of syphilis when the Wassermann test is negative. One must be cautious of accepting relief from surgery as proof of the presence of hyperthyroidism. The neuropathic patient is commonly relieved at least temporarily by any surgical procedure but time will eventually bring out the same or a new train of symptoms. At times the removal of an adenomatous or nodular goiter will give marked relief in the presence of a normal metabolism. In such cases the mechanical relief must not be lost sight of and the normal metabolism may be explained by the taking of iodine or the presence of a

remission period so common in this type of struma. The so-called burned out toxic goiter usually has a normal or near normal rate, but shows extensive clinical evidence of damage due to long standing toxicity.

Hyperthyroidism for the most part is a well defined, yet often not easily diagnosed symptom complex. The most dependable symptoms are (1) definite loss of weight in the presence of a normal or increased food intake, (2) a persistent tachycardia of over 80, (3) a constant feeling of warmth or a sensitiveness to heat. On the other hand symptoms often associated with Graves' disease such as fatigue, sweating, tremor, transient rapid heart rate, choking sensations, loss of weight in the presence of anorexia and sub-normal food intake, nervousness and emotionalism are more often caused by functional disorders of the nervous system than by true thyroid disease. It should always be kept in mind when a goiter is present that nervous symptoms may at times be present and be unrelated to it.

Care should be exercised in diagnosing mild hyperthyroidism with metabolic rates of from +15 to +35 especially if of short duration. These cases should be kept under observation for a time and repeated metabolic studies made. Ultimately normal figures will be obtained in the great majority of these border line cases as is well illustrated in cases V and VI.

The presence of mental symptoms, hysterical seizures, fits of depression, crying spells and marked emotionalism should be a warning that one may not be dealing with thyroid disease. This is well illustrated in case III. Like-

wise marked chronicity of nervous symptoms, especially where there is a marked nervous or mental family tendency, is a factor against the diagnosis of thyroidism

Great caution should be exercised in making a diagnosis of hyperthyroidism in a patient under age 20. Because of the presence of a struma and certain nervous symptoms, the error is often made. The metabolism in this group is often found to be below normal pointing rather to a hypofunction of the thyroid. Surgery is rarely indicated and then only after most careful consideration of the diagnosis

SUMMARY

1 The term Graves' disease, because of its association with the thyroid gland, should be reserved for cases of hyperthyroidism

2 The large neurogenetic group

simulating hyperthyroidism and usually classified under the term Graves' disease should be designated by some other term to indicate its neuropathic origin and to avoid any association with the thyroid gland

3 The basal metabolism test is the most important factor in the diagnosis of hyperthyroidism, when properly performed and interpreted

4 The most dependable symptoms of hyperthyroidism are persistent tachycardia, loss of weight in the presence of a normal or increased food intake and a sensitiveness to heat.

5 Hyperthyroidism should be diagnosed with caution under the following conditions; in the presence of mental symptoms, when symptoms are mild and the metabolic rate is from +15 to +35, when there is marked chronicity of nervous symptoms and in cases under age 20

REFERENCES

- ¹KESSEL, L., LIEB, C. C., and HYMAN, H. T. A study of exophthalmic goiter and the involuntary nervous system, *Jr Am Med Assoc*, 1922, lxxix, 1213-1216
- ²MOSHCOWITZ, ELI. The nature of Graves' disease, *Arch Int Med*, 1930, xli, 610-629
- ³HAMILTON, B. E., and LAHEY, F. H. Differentiation of hyperthyroidism and heart disease from neurasthenic states, *Jr Am Med Assoc*, 1922, lxxviii, 1793-1796
- ⁴BENEDICT, F. G. The measurement and standards of basal metabolism, *Jr Am Med Assoc*, 1921, lxxvii, 247-250
- ⁵DUBOIS, E. F. Basal metabolism in health and disease, 1924, Lea and Febiger, Philadelphia, p. 104
- ⁶ZIEGLER, L. H., and LEVINE, B. S. The influence of emotional reactions on basal metabolism, *Am Jr Med Sci*, 1925, clxix, 68-76
- ⁷LANDIS, C. Studies of emotional reactions, metabolic rate, *Am Jr Physiol*, 1925, lxxiv, 188-203
- ⁸HENRY, G. W. Basal metabolism and emotional states, *Jr Nerv and Ment Dis*, 1929, lxx, 598-605
- ⁹BARACH, A. L., and DRAPER, G. The significance of the basal metabolism determination, *Jr Am Med Assoc*, 1925, lxxxiv, 740-745

Hero Worship and the Propagation of Fallacies

(Lessons from the Lives of Jean Astruc and John Hunter)*†

By C S BUTLER, M D, F A C P, Captain, (M C), U S Navy,
U S Naval Hospital, Brooklyn, N Y

GABRIEL LeClerc in the year 1692 wrote a compend entitled "La Chirurgie Complete" which, according to Garrison went through eighteen editions. The fourth edition was translated into English in 1707, and we will quote part of the title-page of this because of its pleasing quaintness of diction "The Compleat Surgeon or the Whole Art of Surgery explain'd in a most familiar method. Containing an exact account of its principles and several parts, viz Of the bones, muscles, tumours, ulcers, and wounds, simple and complicated, or those by gun-shot, As also of Venereal Diseases, the Scurvy, Fractures, Luxations, and all sorts of Chirurgical Operations. To which is added a Chirurgical Dispensatory, shewing the manner how to prepare all such Medicines as are most necessary for a Surgeon, and particularly the Mercurial Panacea." This must have been a popular compendium of surgery for the students of those days both French and English. The delightful little book gives an excellent dis-

cussion of the venereal diseases, correct as to types with the omission of chancroid which was not defined until 1858. Gonorrhea or the "Chauderpisse" and its complications and syphilis, or the pox, were handled much as they are today. Indeed the treatment of these two diseases is about as effective as it was at the beginning of the twentieth century.

Jean Astruc (1684-1766), celebrated physician of Louis XV was so scholarly at the height of his career that few contemporaries dared oppose him. In addition to writing a critique upon certain parts of the Bible, he gained for himself a well-earned reputation as a literary physician at a time when medicine was emerging from Medievalism. Of his medical works, perhaps the most important was entitled "A Treatise of the Venereal Disease in Six Books." The Latin text of 1736 was translated into English the following year. It has never been understood even by his own countrymen how such a scholar as Astruc could lend himself to the propagation of so much that was fallacious in a single volume. As is well known, he contended that there was only *one* venereal disease and that this had been transferred from America to

*Read at the Annual Meeting of the American Society of Tropical Medicine, New Orleans, Louisiana, November 20th, 1931.

†Received for publication, November 2, 1931.

Europe by Columbus' ships. The whole force of his classical education was exerted to prove these two fallacies forty-four years after LeClerc's first edition, and though his writings were cried down by other scholars of the day, yet it is a matter of history that his work on "the venereal disease" has influenced medical thought and literature down to the present time. So much of an impression did he make upon the medical men of his time and succeeding generations that it requires only a perusal of the volume of John Hunter entitled "*A Treatise on the Venereal Disease*", published in 1786, to see that Hunter not only embraced Astruc's views, but actually the title for his own work. He accepted Astruc's interpretation of the venereal diseases in toto. He puts aside, however, the American origin of syphilis with a sentence, in which it appears that he does not care to consider this feature, though agreeing with Astruc as to the appearance of syphilis in Europe at a recent date.

As to the question of the viruses of gonorrhea and syphilis being the same, Hunter was so positive of the truth of this that in 1767, when he was 39 years of age, he inoculated himself with material from what was probably a urethral chancre though he thought it gonorrhoeal pus. Born in 1728, he died in 1793, and it was evident from his description of his own symptoms and from the write-up of Sir Everard Home on the course of the disease from which he died, that this inoculation influenced his entire future career. Hunter's first attack of angina pectoris occurred in 1773, just about six years after his unfortunate

inoculation. By 1785 he had progressed so far that generalized arteriosclerosis had extended to the point of producing cerebral symptoms, due to arteriolar spasm simulating the Adams-Stokes syndrome. Following a period of unconsciousness, he had twitchings of the muscles of the nose, face, lower jaw, and left arm. This was a fairly typical example of the syphilitic cerebral syndrome. By the year 1789 a type of oculomotor palsy had developed which was most likely syphilitic. Few histories are more pathetic than that of the devotion of this great man to a search for the facts about syphilis. The influence of Astruc, however, is so evident in his case that it needs only a perusal of the two volumes to see that Astruc's views held him captive. Hunter's works are among the great contributions to English medical literature. In turn his force and personality and practical knowledge won many generations of physicians who in turn accepted his word as law.

In a delightful study of the history of certain medical instruments Professor Logan Clendenen¹ describing the revolution which Schonlein and his students effected in the teaching of clinical medicine uses the following phrase: "Happy is that medical school which has on its faculty three or more intensely vivid clinical teachers who hate one another and despise their rival's methods and views. Stimulating is the mental atmosphere of such an establishment." Schonlein, Frerichs, Traube, and Wunderlich in a very brief period revolutionized clinical teaching and gave to medicine a proper estimate of thermometric de-

terminations in disease and of the importance of temperature curves in various infections. The brief history of these two groups shows the relative value of hero worship and of intellectual competition in the search for truth.

In 1816 another great French physician was at the height of his professional career, Doctor A. J. L. Jourdan. In that year he published in the "Journal Universel des Sciences Médicales" five articles entitled "Considerations Historiques et Critiques sur la Syphilis". Jourdan, like Astruc, was also a medical *litterateur*, but Astruc had some seventy-five years advantage in point of time. In these articles Jourdan completely disproves Astruc's ideas in regard to the origin of syphilis, and backs it up with incontrovertible evidence. This gem of medical literature was translated into English by Doctor R. LaRoche in 1823 and published in Philadelphia in that year. It has remained buried there for the past century. In 1826 Jourdan wrote his exhaustive treatise entitled "Traité Complet des Maladies Veneriennes", 2 volumes, Paris, in which he gives all the material concerning the subject under consideration which had come out in the first named publication. Opinions and facts we think quite modern were shown by this French scholar to extend well into the Dark Ages and in some cases into ancient times. While his views upon constitutional syphilis were incorrect, most of his work was sound. In spite of these and other more recent treatises showing the fallacies in Astruc's work, one of these fallacies goes merrily on and at the present

time is held by the majority of physicians of Europe and America. We refer to the American origin of syphilis which Astruc appropriated from Oviedo's book of 1525.

Coming back to Hunter, whose opinions were now considered as infallible, we find that he ventured to express positive views upon matters about which he knew little and to indulge in speculation in a way not calculated to advance a knowledge of medicine. We are speaking now of Hunter, the syphilographer. As a urologist, Hunter was years in advance of his time.

On pages 14 and 15 of his treatise, he attempts to show how "the venereal disease" was introduced into the South Seas. Calling upon the voyages of Captain Cook, who, as is well known, visited most of the island groups of the South Pacific between the years 1768 and 1779, he expressed the view that it was the French under Bougainville, 1766 to 1769, who first introduced the venereal disease into Otaheite (Tahiti) for although Cook visited Tahiti sometime in advance of Bougainville, Hunter convinces himself that it was Bougainville who introduced the venereal diseases into the Society group. As a matter of fact both the English and French fleets were important factors in spreading venereal diseases through the islands of the South Pacific. In connection with Hunter's statements in this regard, we will quote the views expressed by one or two modern writers upon tropical medicine. Manson-Bahr² expresses himself upon the origin of yaws in the following terms: "The home of yaws at the present day is within the true tropics, between

Capricorn and Cancer, its chief ravages are mainly confined to the old world, its distribution in the new (West Indies, Venezuela, Guianas, and Brazil) being directly due to the infamous influence of the slave trade. Thus has Fate decreed that the gift of syphilis from the new world to the old, consequent upon the Spanish Conquest, should be repaid in kind some hundred years later by the exportation of yaws from Africa by negro slaves." In "Tropical Diseases" by the same author³, occurs this sentence in connection with immunity in yaws: "Apparently saturation of a community with yaws virus produces a relative immunity to syphilis. On these grounds may be explained the apparently well authenticated fact that syphilis is *absent* amongst the Polynesians of Fiji, Tonga, and Samoa, in whom yaws is especially prevalent." Now it is axiomatic in the epidemiology of syphilis that there is no place on earth the white man has visited from which syphilis is *absent*, so that Manson-Bahr is but expressing the views of Astruc and Hunter, views of the middle of the eighteenth century, when making these statements in 1928 and 1929. Hunter's remarks upon the origin of "the venereal disease" in the South Sea Islands is but another example of the unscientific, not to say ungenerous, effort to "wish" syphilis off on the people of other races, efforts so common in the fifteenth and sixteenth centuries.

On pages 382 and 383 of the 1786 edition, Hunter speaks with assurance upon yaws. It appears that he saw only one case of this condition in the course of his career and upon this he

makes his positive statements. In this he reminds us very forcibly of certain "library authorities" on yaws at the present time. At this place in his treatise we find such assertions as the following: "Yaws have a regular progress after going through which they leave the constitution in a healthy state at least free from that disease. It being sufficient for the cure that the patient be in a state favorable to general health." This resembles very much some of the 1930 assertions emanating from Manila, that yaws is one of the easiest of all constitutional diseases to cure, assertions made in complacent disregard of the controverting experience of scores of tropical practitioners in other parts of the world. However, I think that Berkeley Hill's sentence about Hunter's *one* case of yaws proves the soundness of someone's belief in the emphasis of understatement. Here is Hill's sentence (Syphilis and Local Contagious Disorders, page 15): "John Hunter writing 'on diseases resembling the lues venerea, which have been mistaken for it', describes a case of yaws that was clearly syphilis, for the very reasons he advances to prove it could not have been that disease." Castellani and Chalmers⁴ writing upon yaws make the statement that the endemic home of yaws is in America and that Sydenham's statement that it is in Africa is not compatible with the facts as now known. "It must be remembered", they remark, "that the discovery of America led to a great many voyages in all directions, and we need not be surprised to find that Bontius in 1718 found the disease to be endemic in Java, Sumatra, and other

Dutch Colonies in the East Indies

In 1832 Bennet stated that it was endemic in the Tonga, Society, and Navigator Islands, while Koeniger believes that its introduction into the Samoan group was comparatively recent. It is therefore possible that it may have spread throughout the tropics from America, both in an easterly and westerly direction." Was it the white crews making the voyages "in all directions" that spread yaws to the Orient? Yaws is *not* a white man's disease. The date, 1832, is over 50 years after Bougainville and Cook. Thus do the authorities on tropical medicine differ very markedly on the geography of yaws and here they are accepting the views of the older writers who knew much less about the facts than we of the present.

There is no way of reconciling the diverse statements and opinions expressed by John Hunter and the others quoted with the facts as known about yaws. Such bizarre, fanciful statements are made by the "yaws experts" in all parts of their description of it from definition to treatment! These fanciful statements make of this condition what we have elsewhere spoken of as a medical monstrosity. The fallacies of these statements have been considered by many writers for all of the divisions of the description of this *impossible* entity. We should like to notice only one more of these inconsistencies having to do this time with the pathological side of the description of yaws. In an article entitled "Yaws, As Observed in Haiti", Doctor Howard Fox⁵ quotes from the laboratory report the following pathological differentiation. "Microscopic examina-

tion of early and late yaws showed an edematous verrucous plasmoma in which the infiltration was horizontally delimited below and was not intimately related to inflamed blood vessels, as in syphilis. Plasma cells were more succulent and larger than in syphilis, giant cells were rare and there was no productive inflammation of the blood vessels." Most of these statements have been disproven or properly evaluated by Choisser and others, but it seems that the pathologist here depends upon the relative "succulence" of the plasmoma cells to enable him to differentiate the histopathological picture of yaws from that of syphilis. One wonders if a "standard of succulence" might not be established in order to aid in such differentiation. The description of the histology of the yaws granuloma harks back to the erroneous conclusions of MacLeod⁶, who compared the framboesoma, *not* with its luetic reflected image, the condyloma and the circinate syphilid, but with the histological picture of syphilides in general. Moreover, MacLeod seems to have labored under the impression that framboesia did not affect the viscera. This is quite erroneous. At the present time there is a considerable amount of autopsy material from cases of Haitian treponematoses being studied in the Department of Pathology of the University of Michigan and it is hoped that this investigation will give us the facts about the histopathology of yaws.

In conclusion, we may say that the effect of the work of Astruc and Hunter upon our knowledge of the venereal diseases has been to confuse

rather than to clarify, to perpetuate fallacy rather than to uncover truth. A comparison of their careers with those of Schonlein, Frerichs, Traube, and Wunderlich leads to the conclusion that in advancing a knowledge of medicine it is better to have open intellectual combat than to have too much scholarship and too much hero worship. It has fallen to the speaker's lot to be unable to accept some of the

current views regarding yaws and syphilis. It is not a pleasant task to be an "image breaker" in this field. Carlyle did not treat of the "Hero as Physician." Had he done so, he might have found several candidates for Hero Worship in tropical medicine. It is our firm belief that when the blight of hero worship is eradicated from tropical medicine, the views of Hutchinson and of Jourdan will prevail.

REFERENCES

- ¹CLENDENING, L. History of certain instruments, *Ann Int Med*, 1930, iv, 176-189
- ²MANSON-BAHR, P. H. Yaws, *Brit Jr Ven Dis*, 1928, iv, 44-54
- ³MANSON-BAHR. Tropical diseases, 1929, William Wood and Company, New York, p 500
- ⁴CASTELLANI, A., and CHALMERS, A. J. *Frambesia tropica*, (Yaws), The practice of medicine in the tropics, Byam and Archibald, 1922, ii, Henry Frowde and Hodder and Stoughton, London, p 1309
- ⁵FOX, H. Yaws (*frambesia tropica*) as observed in Haiti, *Arch Dermat and Syph*, 1929, xx, 820-834
- ⁶MACLEOD, J. M. H. Contribution to the histo-pathology of yaws, *Brit Med Jr*, 1901, 797-803

Editorial

THE JOHN PHILLIPS MEMORIAL PRIZE

It is with very sincere pleasure, indeed, that announcement is made elsewhere in this issue, in the form of an excerpt from the Minutes of the December meeting of the Regents of the American College of Physicians, of the award of The John Phillips Memorial Prize to Doctor Oswald T Avery. This award is in recognition of the work of Dr Avery on the capsular polysaccharides of the pneumococci, leading to the production of an enzyme having a specific and selective action upon the Type III polysaccharide, both in the chemically pure state and as it

exists in the capsules of the living pneumococci. Further, Dr Avery has shown that mice, injected with an active preparation of the enzyme together with multiple lethal doses of a virulent culture of Type III pneumococcus, survive infection. The specific enzyme, by decomposing the capsular polysaccharide, apparently renders the infecting organism vulnerable to the defensive mechanisms of the animal body. Thus a new mode of attack upon the causal agencies in the infectious diseases is opened for experimental investigation.

THE LYMPHOID TISSUE CHANGES IN THE PRO- DROMAL STAGE OF MEASLES

In a paper which was not published until after his death, Warthin¹ described the occurrence of large multinucleate giant cells in the tonsils of four patients who subsequently developed measles. In each instance, as afterwards appeared, tonsillectomy had been performed from twenty-four to ninety-six hours before the appearance of the exanthem. So characteristic were the histopathological findings

that they were used successfully in the later cases of the series to predict the onset of measles before clinical evidence was available. One child was removed from an open ward and placed under contagious disease precautions on the strength of the pathological diagnosis alone, and the subsequent appearance of the eruption justified the confidence which the clinician had placed in the diagnosis made by the pathologist. The essential pathological lesion in the tonsils and pharyngeal mucosa in the prodromal stage of measles was found to be a subepithelial infiltration of multinucleate giant cells, lymphocytes and monocytes, with wandering of the giant cells into the mucosa and on to its surface. The germinal centers of the lymphoid

¹WARTHIN, ALDRED SCOTT. Occurrence of numerous large giant cells in the tonsils and pharyngeal mucosa in the prodromal stage of measles, *Arch of Path*, 1931, x1, 864-874.

follicles were found to show lymphoid exhaustion and here, also, numerous multinucleate giant cells were present. A cervical lymph node from one of these patients, examined after recovery from measles, showed no similar changes. That these changes are not confined to the tonsils and pharyngeal mucosa is evident from a recently reported observation of Herzberg.² On the fourth day after an appendectomy a child developed a rash on the face, body, and extremities, with Koplik spots, conjunctivitis and cough. A definite diagnosis of measles was made. In several of the lymph follicles of the appendix, but apparently in a sharply localized area only, there were found multinucleate giant cells. From the description and illustrations of these giant cells and the associated hyperplasia and lymphoid exhaustion of the germinal centers, it seems certain that Herzberg has found in the appendix during the prodromata of measles the same lesion which Warthin found to be pathognostic of the onset of this disease when seen in the pharyngeal mucosa and tonsils. This provides evi-

dence of a more general invasion of the lymphadenoid tissues during the onset of measles than had hitherto been demonstrated. It is to be hoped that others will search for these apparently highly significant histological changes when opportunity is presented.

PROGRAM OF THE SAN FRANCISCO MEETING

In the College News Notes section of this issue will be found the final program of both the General and the Clinical Meetings of the Sixteenth Annual Clinical Sessions of the American College of Physicians. Fellows and Guests expecting to attend will find it highly advantageous to observe the directions which are included having to do with transportation, reservations, and registration for Clinics and Demonstrations. In richness of material, breadth of interest and skill in arrangement, these programs give evidence, on the one hand, of the unselfish labors of those whose task it was to assemble them, and, on the other, of the great wealth of material for didactic and clinical medicine which San Francisco and its Pacific Coast neighbors possess. An unusually profitable meeting is in prospect for all who can attend.

²HERZBERG, MORTIMER. Giant cells in the lymphoid tissue of the appendix in the prodromal stage of measles: report of an isolated case, Jr Am Med Assoc, 1932, xcvi, 139-140.

Abstracts

The Detection and Estimation of Radium in Living Persons III The Normal Elimination of Radium By HERMAN SCHLUNDT and G FAILLA (Am Jr Roentgenol and Rad Therap, 1931, xxvi, 265-271)

Using as subjects two girls who had contracted radium poisoning during employment as dial painters during the period 1917 to 1919, the authors determined the rate of elimination of radium by determining the total quantity of radium present in each subject, as well as the quantity eliminated each day. The first of these values was arrived at by making gamma-ray measurements on the subjects by means of a standardized electrometer and adding to the value thus obtained the quantity of radium responsible for the radium emanation (radon) found present in the air expired. Combining all the experimental results, it appeared that the radium content of Subject A, twelve years after exposure, was 24 μg , and of Subject B, 14 μg . The quantity of radium removed day by day by excretion was determined by estimations, about 90 per cent of the amount eliminated being found in the feces. The total radium eliminated daily by Subject A amounted to 1161 μg , corresponding to a coefficient of daily elimination of 0.005 per cent. The total daily elimination of Subject B was 363 μg , giving a coefficient of daily elimination of 0.0026 per cent. Possible reasons for the difference in the coefficients for the two subjects are discussed. It is of interest that reduction by the process of natural decay of the element need not be considered practically in the case of radium stored in human body, for its half period is about 1600 years. The experiments reported show, therefore, that radium continues to be eliminated even twelve years after ingestion, although the rate of elimination is very slow. They also show that most of the radium eliminated is found in the feces. The results throw considerable doubt

upon the validity of the assumption that the stored radium is distributed uniformly throughout the skeleton.

Involvement of the Central Nervous System in a Case of Glandular Fever By SAMUEL H EPSTEIN, M D, and WILLIAM DAME-SHEK, M D (New England Jr Med, 1931, ccv, 1238-1241)

Severe headache, blurring of vision, photophobia, and general malaise had marked the onset of disease in a young man, 19 years old, who was admitted to the hospital in a stuporous condition. The spleen could be felt and there was a generalized enlargement of the lymph nodes. The total white blood cell count was 14,900 per cubic millimeter, with 63 per cent lymphocytes and 8 per cent monocytes. In all respects the morphology of the blood was typical of that occurring in infectious mononucleosis. Lumbar puncture yielded a clear, colorless fluid under normal pressure. On admission there were 34 white cells per cubic millimeter, chiefly lymphocytes. This number rose to 44 eight days later, but after that time gradually decreased, falling about proportionately with the decrease in white cells in the blood. Culture of the spinal fluid showed no growth and the Wassermann reaction was negative. The subsequent clinical course, resulting in complete recovery, served to rule out certain possibilities in the differential diagnosis, particularly acute lymphatic leukemia and tuberculous meningitis. It appears obvious that in this case the acute neurological condition and the general lymphoid hyperplasia with mononucleosis must be closely related. The nature of this relationship cannot be answered completely at present. The close parallelism between the cellular changes in the cerebrospinal fluid and the changes in the leukocyte count is significant. The simultaneous clinical recovery and the return to normal of the white blood cells indicate at least a temporal relationship so that it is not

unreasonable to suppose that the same infectious agent which caused the lymphoid hyperplasia also produced the central nervous system condition. Johansen has recently reported a similar case emphasizing the relationship between serous meningitis and infectious mononucleosis.

Renal Lesions in the Toxemias of Pregnancy By E. T. BELL, M.D. (The Am Jr Path, 1932, viii, 1-41, 3 plates)

Twenty cases of toxemia of pregnancy were divided into five groups: (1) typical eclampsia with convulsions, (2) eclampsia without convulsions, (3) pre-eclampsia, (4) hyperemesis gravidarum, and (5) pregnancy in association with pre-existing renal disease. The pathological changes found in these patients at autopsy are detailed with special attention to the kidneys. In fatal cases of eclampsia and pre-eclampsia a characteristic glomerular lesion was found. The glomeruli were found to be slightly enlarged and the lumina of their capillaries narrowed. The decrease in size of the capillary lumina is caused chiefly by a marked thickening of the capillary basement membrane, but sometimes by an increase of endothelial cells. In one patient, who had had an attack of eclampsia seven years before, focal hyaline areas were found in the glomeruli with partial or complete glomerular obliteration and varying degrees of tubular atrophy. In one case of hyperemesis gravidarum, glomerular lesions were found like those of typical eclampsia. In three other cases the glomeruli were normal. A fatty liver without necroses is characteristic of this form of toxemia. When a woman with chronic renal disease becomes pregnant, there is usually an aggravation of all the nephritic symptoms. Chronic nephritics show no special tendency to develop gestation eclampsia.

The Influence of Solar Rays on Metabolism, With Special Reference to Sulphur and to Pellagra in Southern United States By JAMES H. SMITH, M.D. (Arch Int Med, 1931, xlviii, 907-1063)

Sulphur in the form of cystine appears to exert a protective action against exposure to solar radiation in low forms of life. Its high concentration in the epidermal tissues

of higher animals suggests a possible protective action here also. Thus it appears that an adequate supply and a normal metabolism of sulphur exert a preventive influence against the pathologic effects of solar irradiation. Conversely, it is suggested that an inadequate supply of sulphur as cystine is an important cause of pellagra. Further, the distribution of pellagra and the variations in its prevalence and incidence suggest that solar irradiation, under certain abnormal conditions of nutrition, is an important factor in the etiology of pellagra, and that the reaction to solar rays not only is conditioned by the nutritive state, but depends on a state of the tissues determined by contrasts in degree and intensity of exposure during the annual cycle.

A Clinical Study of Myxedema in Michigan By H. H. RIECKER, M.D. (Jr Mich State Med Soc, 1931, xxx, 831-835)

From a study of the geographical distribution of 64 cases of myxedema in the series studied, and in comparison with the usual clinical experience in other regions, it is concluded that this disease is more common in the Great Lakes goiter district than in non-goitrous regions. In the series studied, 75 per cent of the patients were female, and 34 of the 64 were in the age-group 41-60. In 40 per cent the basal metabolic rate was between 15 per cent and 25 per cent below normal. The most common presenting symptom of the patients in this group was weakness. One organ or system was frequently noted to present outstanding signs or symptoms. Anemia, skin lesions, mental and cardiac complaints, and digestive disturbances illustrated this point. Obesity emphasizes rather than submerges the characteristics of the disease.

Über vorübergehende Hemiplegien durch Nicotin [Transitory Hemiplegia Due to Nicotine] By F. KULBS (Klin Wochenschr, 1931, x, 2159-2161)

In four cases, three men whose ages were between 21 and 38 years and a woman 40 years old, transitory paralytic phenomena appeared. In the three men these consisted of hemiplegia and speech disturbances. In the woman there was a motor aphasia. These

disturbances had been preceded by evidences of lessened functional capacity as shown by ease of fatigue, or by headache, paresthesia and dizziness. In all cases there had been gross overuse of tobacco, evidence of which was found in lymphocytosis, elevated basal metabolic rates and marked nervous and vasomotor irritability. Since there was a complete restoration to normal in all cases within a short time of the interdiction of

the use of tobacco, it is believed that the hemiplegic phenomena were due to a vasoconstrictor effect of tobacco. Acute fatigue, hereditary factors and syphilis could all be excluded with certainty as etiological agents. This observation may be a significant contribution in respect to that group of cases which shows hemiplegia clinically, without anatomical changes adequate to explain its occurrence.

Reviews

Recent Advances in Allergy (Asthma, Hay-Fever, Eczema, Migraine, etc.) By GEORGE W. BRAY, M.B., C.M. (Sydney) Asthma Research Scholar, The Hospital for Sick Children, Great Ormond Street, London. With foreword by ARTHUR F. HURST, M.A., M.D. (Oxon), F.R.C.P., Senior Physician, Guy's Hospital, Chairman Medical Advisory Committee, Asthma Research Council of Great Britain. 432 pages, 98 illustrations, including 4 colored plates. P. Blakiston's Son & Co., Inc., 1012 Walnut St., Philadelphia, 1931. Price, \$3.50.

The author's two years of research in asthma at the Hospital for Sick Children have evidently given him a wide experience with allergic disease. He reviews the important theories and surveys the large field of experimental work. Brief historical sketches are also interspersed. He discusses heredity and the endocrines as factors in the causation of allergy. The more usual manifestations of allergy, as asthma, hay-fever, eczema, urticaria and angioneurotic edema are taken up in some detail. Numerous other conditions, such as dermatitis venenata, migraine, epilepsy, muco-membranous colic, vaccine therapy, drugs, serum reactions, hypersensitiveness to insects, the effects of molds and fungi, are discussed as to their known and possible relation to allergy. Addition and elimination diets are given. This book gives a fairly complete treatment of the subject, written in a compact form, and in a clear, easily read style. Unfortunately, all pollination data are for the British Isles. So significant is geographical distribution

and pollination chronology in the botanical aspect of allergy, that it would be well to have an American edition when reprinting is undertaken.

The Human Voice By LEON FELDERMAN, M.D., x + 301 pages, 22 figures. Henry Holt and Company, New York City, 1931. Price, \$2.50.

There is probably no medical book more difficult to write than that which endeavors to expound medical matters to lay readers. And there is no book which requires any greater degree of precision and accuracy in statement, for it must be assumed that the group for whom it is intended will be altogether unable critically to evaluate it. It is stated in the book under review that it is intended to bridge the difficulties between the vocal teacher and his pupil and that "a sincere effort has been made to strip discussions of technical terms and to write in a language familiar to all." In regard to the sincerity of the author and the innocence of the publishers there can be no question. The introduction of such terms as [in the actual spellings used] archi pallium, kinaesthetic, laryngo-periskop, pharmacotoxic, lancelating, streptococcic hemolyticus, and non-memolytic, leaves some doubt as to whether the language is understandable by all. More serious are actual errors in fact, stated or implied. Some of these are of an extraordinary nature. For instance, in regard to the possible spread of syphilis by unsanitary lunch rooms and soda fountains, it is stated that "Hordes of flies gather, ready to carry the *larvae* from one place to another, and the vicious circle of

contagion is maintained" The combination of syphilis as a fly-borne disease and of the Treponema as a larva in the same sentence compels a pause even from one who is accustomed to grading examination papers The author is evidently a believer in the efficacy of maternal impressions in the etiology of disease, for he lists among the causes of stammering, a fright or a profound disappointment experienced by the mother during the prenatal period Scientific medicine has been striving for several decades to release the human mind from the bondage of such erroneous ideas Thus the reviewer is forced to the conclusion that to be both useful and safe this book requires extensive revision

Confessio Medici By STEPHEN PAGET, F R C S, Late Vice Chairman Research Defense Society xi + 158 pages The Macmillan Company, New York City, 1931 Price, \$2.00

Again these charming essays are made available for the general medical reader Published in 1908, this reissue brings them to a new generation of physicians They can never grow old for they are of the medical life itself Vocation, Hospital Life, An Essay for Students, A Good Example, Practice, The Discipline of Practice, The Spirit of Practice, Wreaths and Crosses of Practice, Retirement, and The Very End are the titles of the series, with a Preface and an

Epilogue Since each essay is complete in itself this is a book to be picked up in the moment of leisure when the available time is short or to be taken along as a companion on a journey The publishers are to be commended for bringing out this new issue

Guide to Radiologic Diagnosis in Heart Disease Prepared with the Aid of the Committee on Research of the Heart Committee By GEZA NEMET, M D 33 pages, 31 figures New York Tuberculosis and Health Association, Inc., 386 Fourth Avenue, New York City, 1931 Price, 35 cents

A concise system for the interpretation of roentgenograms of the heart is set forth in the interest of securing suitable technical procedures and a more uniform nomenclature

Criteria for the Interpretation of Electrocardiograms Prepared with the Aid of the Committee on Research of the Heart Committee By ARTHUR C DEGRAFF, M D, 19 pages, 42 figures New York Tuberculosis and Health Association, Inc., 386 Fourth Avenue, New York City, 1931 Price, 35 cents

This is a concise statement of criteria in electrocardiography arranged by diagnoses and by terminology

College News Notes

THE PHILLIPS MEMORIAL PRIZE

The following announcement is an excerpt from the minutes of the meeting of the Board of Regents held December 20, 1931

"Dr Means, Chairman of the Phillips Memorial Prize Committee, reported that his Committee had proceeded according to the revised regulations adopted by the Board of Regents, which were, briefly, that the Committee seek a candidate for the prize rather than invite submission of manuscripts as had been done the year before. After discussing the procedure of his Committee, he presented the name of Dr O T Avery, Hospital of the Rockefeller Institute for Medical Research, New York City, with the recommendation to the President that the prize be awarded to Dr Avery for the series of studies upon the pneumococcus in which he has played a leading rôle, beginning with the discovery of the type specific soluble capsular polysaccharides and culminating in the discovery of a bacterium which produces an enzyme which splits the polysaccharides of Type III pneumococcus in vitro, thus rendering it susceptible to phagocytosis and thereby protecting the animals which are infected with it'

"This recommendation was adopted unanimously

"President White stated that if it could be arranged, Dr Avery's presentation should be made at the time of the Convocation, and preceding the Presidential Address, to which the Board agreed"

Acknowledgement is made of the receipt of gifts to the College Library of publications by members, as follows

Dr Henry Daspi (Fellow), New Orleans, La, 1 autographed copy, No 54, "Matas Birthday Volume",

Dr Hyman I Goldstein (Associate), Camden, N J, 1 reprint,

Dr H Beckett Lang (Fellow), Marcy, N Y, 5 reprints,

Dr William D Reid (Fellow), Boston, Mass, 3 reprints,

Dr Walter M Simpson (Fellow), Dayton, Ohio, 1 reprint, "Aldred Scott Warthin",

Dr Charles T Way (Fellow), Cleveland, Ohio, 1 reprint,

American College of Surgeons, 1 copy of 1932 Directory

Dr Frank Smithies (Master), Chicago, Ill, presented a medical clinic before the Mahoning County Medical Society at the Youngstown, Ohio, Hospital, October 20, and on the evening of the same date, addressed the Mahoning County Medical Society on "Gastric Hemorrhage"

Dr Louis Faugeres Bishop (Fellow), New York City, as one of the Trustees of Rutgers University, has been assigned to the Governing Committee of the New Jersey College of Pharmacy, Newark, N J. The College will give a four year course leading to the degree of B S in Pharmacy. The course will cover the requirements of the American Medical Association of a pre-medical course for those students who may wish later to study medicine.

Dr D N Kremer (Fellow), Philadelphia, Pa, addressed the Bay Ridge Medical Society, Brooklyn, N Y, December 8, on "Obesity and Its Management"

Dr I S Kahn (Fellow), San Antonio, Texas, in collaboration with Dr B F Stout of San Antonio, read a paper entitled, "The Practical Value of the Cytological Examination of the Nasal Smear in the Differential Diagnosis Between Allergy and Infection (Preliminary Report)," at the recent meeting of the Southern Medical Association

Dr W J Stapleton, Jr (Fellow), Detroit, Mich, gave a lecture on "Medicine in Art" before the Detroit Medical Club on December 17, 1931

Dr Stapleton also gave a radio talk on the subject, "Periodic Health Examination" over Station WWJ, January 5, 1932

Dr Ralph Pemberton (Fellow), Philadelphia, Pa, recently gave a paper on "Arthritis" at the Annual Clinic of the Sectional Meeting of the Michigan State Medical Society at Jackson, Mich

Dr Horace W Soper (Fellow), St Louis, Mo, read a paper on "Roentgen Diagnosis of Lesions in the Small Intestine," with x-ray illustrations, before the Radiological Society of North America on December 1, 1931

Medical Clinics by the following Fellows of the College were published in the December Number of the Hahnemannian Monthly

Dr G Harlan Wells, Philadelphia, "Trichiniasis",

Dr Carl V Vischer, Philadelphia, "Bronchial Asthma",

Dr Donald R Ferguson, Philadelphia, "Chronic Valvular Heart Disease of Rheumatic Origin with Passive Congestion"

Dr John R Vonachen (Fellow), Peoria, Ill, was recently elected President of the Peoria County Medical Society

Dr Ada E Schweitzer (Fellow), Indianapolis, Ind, Child Hygiene Director of the Indiana State Board of Health, has recently issued several interesting and helpful bulletins, promoting infant and child hygiene and health in that state

Dr Clyde L Cummer (Fellow), Cleveland, Ohio, has recently published the third edition of "Manual of Clinical and Laboratory Methods," through Lea & Febiger, Philadelphia

Dr Cummer is the author of an article entitled, "Lupus Erythematosus in Infancy and Childhood," Archives of Dermatology

and Syphilology, 1931, XLIV, 999-1032 This article was originally read at the meeting of the American Dermatological Association at Toronto during 1931.

Dr Robert E Ramsay (Fellow), Pasadena, Calif, has recently been elected President of the Pasadena Branch of the Los Angeles Medical Association

Dr Joseph H Bryan (Fellow), Asbury Park, N J, has been elected President of the Alumni Association of the New York Homeopathic Medical College and Flower Hospital Dr Bryan was a member of the graduating class of 1890 of that institution

Dr W G Herrman (Fellow), Asbury Park, N J, read a paper entitled "Varieties of Pulmonary Spirochetosis" before the American Roentgen Ray Society, at their last meeting in Atlantic City Dr Herrman also published an article entitled, "Uterine Hemorrhage Radiologically Considered," in a recent issue of the Journal of the New Jersey State Medical Society

Dr Harold S Davidson (Fellow), Atlantic City, N J, has been elected President of the Atlantic County Medical Society for the year 1932

Dr W H Fairbanks (Fellow), Freehold, N J, has been appointed a member of the Executive Committee of the Monmouth County Medical Society He has been a member of the Board of Health of Freehold for five years

Dr W G Richards (Fellow), Billings, Mont, recently conducted for the Indian Department a tuberculosis survey of the Crow and Cheyenne Indians

At the national meeting of the Milwaukee Academy of Medicine on January 12, the following Fellows of the College were elected

Dr R W Blumenthal, President,
Dr C H Stoddard, Vice President,
Dr Francis D Murphy, Membership Committeeman,
Dr J Gurney Taylor, Chairman, Milk Committee

Dr Samuel A Levine (Fellow), Boston, Mass, will be the Guest Speaker on a Symposium on Coronary Disease, in connection with the General Medicine Section of the California State Medical Association meeting at Pasadena during the first week of May

Dr R Manning Clarke (Fellow), Los Angeles, Calif, is Secretary of this Section

Dr Hay M Balyeat (Fellow), Oklahoma City, Lecturer on Diseases Due to Allergy, University of Oklahoma Medical School, addressed the Hot Springs Academy of Science at Hot Springs National Park, February 2, on the subject "Recent Advances in Allergy"

Dr Wardner D Ayer (Fellow), Syracuse, New York, was recently elected President of the Syracuse Academy of Medicine

Dr Earle E Mack (Associate), Syracuse, New York, was recently elected Secretary of the Syracuse Academy of Medicine, and was also re-elected to the Secretaryship of the Onondaga (County) Medical Society

Dr Joseph H Barach (Fellow) addressed the Valley Medical Society, Glassport, Pa, January 21, 1932 Dr Barach's subject was "Clinical Interpretation of High Arterial Pressure"

OBITUARIES

DR RALEIGH PETER HALE

Dr Raleigh Peter Hale (Fellow), East Chicago, Indiana, died December 1, 1931, of heart disease, aged 48 years

Dr Hale was born at Columbia, Mo, attended Northwestern University, from which he received his medical degree in 1908 He was a member of the Indiana State Medical Association, and a past President of the Lake County Medical Society He was elected a Fellow of the American College of Physicians on February 24, 1926

DR ADAM CLARKE DAVIS

Dr Adam Clarke Davis (Associate), Creighton, Pa, died December 13, 1931, age, 62 years Dr Davis graduated from the University of Pittsburgh School of Medicine in 1894 He was a member of the Allegheny County Medical Society, the Medical Society of Pennsylvania and the American Medical Association He became a member of the American Congress on Internal Medicine on March 13, 1925, by virtue of which membership he was transferred to Associateship in the College at the time of the merger of the two organizations during 1926

PROGRAM SIXTEENTH ANNUAL CLINICAL SESSION OF THE AMERICAN COLLEGE OF PHYSICIANS

San Francisco, Calif, April 4-8, 1932

S Marx White, President
General Sessions

Wm J Kerr, General Chairman
Clinical Program

E R Loveland, Executive Secretary
133-135 South Thirty-sixth Street,
Philadelphia, Pa

GENERAL AND HOTEL HEADQUARTERS PALACE HOTEL, New Montgomery
and Market Sts, San Francisco, Calif

Registration headquarters, information bureau, railroad office, exhibits and the general
assembly hall will be located here This hotel will also be the Official Headquarters
Members and guests are asked to make their reservations promptly

LIST OF SAN FRANCISCO HOTELS

Name and Location of Hotel	RATE PER DAY						Extra Person
	No of Rooms	Single Room 1 Person With Bath	Without Bath	Double Room 2 Persons With Bath	Without Bath	Twin Beds	
Palace, Market and New Montgomery	600	3 50 to 7 00		6 00 to 9 00		7 00 to 10 00	2 00
*Alexander Hamilton, 631 O'Farrell St	500	\$3 50 to \$5 00		\$4 00 to \$6 00		\$5 00 — \$6 00	\$1 50
Ambassador, Eddy and Mason Sts	150	2 50 — 3 00	\$1 50 — \$2 00	3 50 — 4 00	\$2 50	4 00 — 5 00	1 00
Argonaut, 4th and Market Sts	400	2 00 — 2 50	1 50 — 2 00	3 00 — 3 50	2 00 — 2 50	3 50 — 4 00	1 00
Bellevue, Geary and Taylor Sts	300	2 50		4 00		5 00	1 50
Brayton, 50 Turk St	110	1 75 to 2 50	1 25 — 1 50	2 00 to 3 00	1 75 — 2 00	3 00 — 3 50	50
Californian, 405 Taylor St	325	3 00 to 4 00		4 00 to 6 00		5 00 — 6 00	1 00
Canterbury, 750 Sutter St	250	2 50 to 4 50		3 50 to 5 00		4 50 to 6 00	1 00
Cartwright, 524 Sutter St	130	2 00 to 2 50		2 50 — 3 00		4 00	1 00
Chancellor, 433 Powell St	150	2 50		3 50		4 00	1 00
Clark, 217 Eddy St	140	2 00 — 2 50	1 50	2 75 to 3 50	2 50	3 50	1 00
Clift, Geary at Taylor St	540	3 00 to 5 00		5 00 to 7 00		6 00 to 8 00	2 00
Colonial 650 Bush St	150	2 50	1 50	3 00 — 3 50	2 00	4 00	1 00
Continental, 127 Ellis St	186	2 00	1 50	3 50	2 50	3 50	50
Court, 555 Bush St.	133	2 00 — 2 50	1 50	3 00 — 3 50	2 00	3 50 — 4 00	1 00
Dale Tallac, 140 Ellis St	152	2 00	1 00 up	2 50	1 50 up		50
Dalt, 34 Turk St	180	1 50 — 2 00	1 00 — 1 50	2 00 — 2 50	1 50 — 2 00		50
El Drisco, 2901 Pacific Ave at Broderick	65	3 00	1 50	4 00	3 50 — 4 50	5 00	1 00
*El Mirasol, 30 Franklin St	105	1 50 — 2 00	1 00	2 00 — 2 50	1 50		50
Fairmont, California and Mason Sts	500	3 50 to 8 00		5 00 to 10 00			2 00
Federal, 1087 Market St	174	2 00 to 2 50	1 25 1 50	2 50 to 3 00	1 75 — 2 00	2 50 to 3 50	50
Fielding, Geary and Mason Sts	105	2 50 — 3 00		3 50 — 4 00		4 00 — 5 00	1 00
Franciscan, 352 Geary St	175	2 00 — 2 50	1 50	2 50 — 3 00	2 00	4 00	1 00

*Also Hotel Apartments

Name and Location of Hotel	RATE PER DAY						
	No of Rooms	Single Room 1 Person		Double Room 2 Persons		Twin Beds	Extra Person
		With Bath	Without Bath	With Bath	Without Bath		
Gaylord, 620 Jones St	200	3 50		5 00		6 00	1 50
Glenburn, 246 McAllister St	65	2 00		2 50		3 00	1 00
Golden State, Powell and Ellis Sts	181	2 00	1 50	3 50	2 50	3 50	50
Governor, 180 Turk St	150	2 00 — 2 50		2 50 — 3 00		3 50 — 4 00	1 00
Herbert's Bachelor, 151 159 Powell St.	108	2 00	1 50	3 00	2 50	3 50	1 00
*Huntington, 1075 California St	144	3 50		5 00		5 00 — 6 00	2 00
Keystone, 54 4th St	168	2 00 to 2 50	1 25 — 1 50	2 50 to 3 00	1 75 — 2 00	3 50	50
King George, 334 Mason St	200	2 00		2 50		3 50	50
Lankershim, 55 - 5th St	350	2 00 — 2 50	1 25 — 1 50	2 50 — 3 00	1 50 — 2 00	3 00 — 3 50	50
La Salle, 225 Hyde St	125	2 00 — 2 50		2 50 — 3 00		3 50 — 4 00	50
Lombard, 1015 Geary St	102	2 00 to 2 50		3 00 to 3 50		4 00	1 00
Mark Hopkins, 999 California St	500	4 00 to 8 00		6 00 to 12 00		7 00 to 14 00	2 00
Maryland, 490 Geary St	84	1 75	1 50	2 25	2 00	2 75	50
Maurice, 761 Post St	150	3 00 to 4 00		4 00 to 5 00		5 00 to 6 00	1 00
Olympic, 230 Eddy St	250	2 00 — 2 50		3 00 — 3 50		4 00	1 00
Oxford, Market and Mason Sts	90	2 00 to 3 00		2 50 to 3 50		4 00	50
Pickwick, 5th near Market St	200	2 00 — 2 50		3 00 — 3 50		4 00	1 00
Plaza, Stockton and Post Sts	300	2 50	2 00	3 50	3 00	4 50 — 5 00	1 00
Powell, 17 Powell St	205	2 00 — 2 50	1 50	2 50 — 3 00	2 00	3 50	50
Ramona, 174 Ellis St	120	2 00		2 50		3 00	50
Roosevelt, Jones at Eddy St	200	2 00 — 2 50		2 50 to 3 50		3 50 — 4 00	1 00
St. Andrew, 440 Post St	60	2 00	1 50	2 50	2 00	3 50 — 4 50	1 00
St Francis, Powell and Geary Sts	1000	3 50 to 8 00		5 00 to 9 00		7 00 to 12 00	2 00
Senate, 467 Turk St	96	2 00	1 50	2 50 — 3 00	2 00	3 00 — 3 50	50
Senator, 519 Ellis St	120	2 00 — 2 50		2 50 — 3 00		3 00 — 3 50	50
Shaw, 1112 Market St	150	2 50		3 00		3 50	1 00
Sir Francis Drake, Sutter and Powell	600	3 50 to 5 00		5 00 to 7 00		6 00 to 8 00	2 00
Spaulding, 240 O'Farrell St	132	2 00 — 2 50	1 50 — 2 00	2 50 — 3 00	2 00 — 2 50	4 00	50
Stewart, 353 Geary St	400	2 00 to 3 00	1 50 to 2 50	3 50 to 5 00	2 50 — 3 00	4 00 to 5 00	1 00
Stratford, 242 Powell Sts	110	2 00 — 2 50	1 25 — 1 50	2 50 to 3 00	1 75 — 2 00	3 00 — 3 50	50
Sutter, Kearny and Sutter Sts	232	2 00 to 3 00	1 50	2 50 to 3 50	2 00	4 00	50
Washington, Grant Ave and Bush St	200	2 00 to 3 00	1 50 — 2 50	2 50 to 3 50	2 00 — 2 50	4 00	1 00
Whitcomb, Market and 8th Sts	500	2 50 to 4 00	2 50 to 3 50	4 00 to 6 00	3 00 to 4 00	4 00 to 6 00	1 50
Willard, 161 Ellis St	125	2 00 — 2 50	1 50	2 50 — 3 00	2 00	3 50 — 4 00	1 00
*William Taylor, McAllister and Leavenworth Sts	500	3 00 to 5 00		4 00 to 7 00		4 00 to 7 00	
Wiltshire, 340 Stockton St	119	2 00 to 3 00		2 50 to 4 00		4 00	1 00
Worth, 641 Post St	96	2 00		2 50			1 00

WHO MAY REGISTER—

- (a) All members of the American College of Physicians in good standing for 1932
- (b) All newly-elected members
- (c) Members of the San Francisco County Medical Society, without registration fee, upon presentation of their 1932 membership cards in their local society
- (d) Medical students pursuing courses at the University of California Medical School and the Stanford University School of Medicine, upon presentation of matriculation cards or other evidence of registration at these institutions
- (e) House Officers of the hospitals participating in the program
- (f) Members of the Medical Corps of the Public Services of the United States and Canada, without fee, upon presentation of evidence of their appointments
- (g) Qualified physicians who may wish to attend this Session as visitors. Such visiting guests shall pay a registration fee of \$15.00, and shall be entitled to one year's subscription to "Annals of Internal Medicine" (in which the proceedings will be published), included within said fee

REGISTRATION BLANKS FOR ALL SPECIAL CLINICS AND DEMONSTRATIONS are sent to members with the official program. Guests may secure a copy of the program by request to the Executive Secretary.

TRANSPORTATION to and from the San Francisco Clinical Session has been arranged on the Identification Certificate plan of fare and half fare. With the exception of the southeast territory, this reduced rate applies for return by diversified routes. In the southeast territory, members must return by the same as the going route, in order to secure the fare and half fare rate. For diverse return routes in the southeast, the fare will be one and three-fifths of the one way tariff.

Reduced fares apply not only to members, but also to dependent members of their families.

Before purchasing tickets, members must secure from the Executive Secretary an Identification Certificate, to entitle them to the reduced fares.

In general, tickets will be sold from March 26 to April 8, with a return limit of thirty days in addition to date of sale. The fare for children of five, and under twelve, years of age will be one-half of the round trip fare for adults. Children under five years of age free when accompanied by parent or guardian. Stop-overs will be allowed at all stations within final limit on either going or return trip, or both, on application to conductors.

All tickets must be validated by a special railroad agent at the San Francisco headquarters from April 4 to 8.

Official itinerary of special train and post-convention tour. Arrangements have been made for a special train from the East to San Francisco, over the Baltimore & Ohio, Chicago & Northwestern, Union Pacific and Southern Pacific Railroads. Following the Session it will proceed over the Southern Pacific, Santa Fe and Baltimore & Ohio railroads back East, according to the following schedule, which has been arranged for the greater comfort and pleasure of members en route. A special booklet has been distributed to every member.

SCHEDULE

Lv New York (West 23d St Station), B & O R R	10 32 A M—March 31
Lv New York (42d St Station), B & O R R	10 10 A M—March 31
Lv New York (Liberty St Station), B & O R R	10 48 A M—March 31
Brooklyn, Liberty Street Coach Route	
Lv Brooklyn (Joralemon Street Station), B & O R R	10 10 A M—March 31

Lv Liberty Street Station, B & O R R	10 48 A M—March 31	
Lv New York (Jersey City Station Capitol Limited)	11 00 A M—March 31	
Lv Newark (Motor Coach Connections), B & O R R	10 55 A M—March 31	
Lv Elizabeth, B & O R R	11 16 A M—March 31	
Lv Philadelphia, B & O R R	12 55 P M—March 31	
Lv Wilmington, B & O R R	1 28 P M—March 31	
Lv Baltimore (Mt Royal Station), B & O R R	2 48 P M—March 31	
Lv Baltimore (Camden Station), B & O R R	2 55 P M—March 31	
Lv Washington, D C, B & O R R	4 05 P M—March 31	
Lv Cumberland, B & O R R	7 20 P M—March 31	
Lv McKeesport, B & O R R	10 39 P M—March 31	
Lv Pittsburgh (Fort Pitt Limited), B & O R R	9 30 P M—March 31	
Lv Youngstown, B & O R R	11 42 P M—March 31	
Lv Akron, B & O R R	12 58 A M—April 1	
Ar Chicago, B & O R R	(C T) 8 05 A M—April 1	
Ar Chicago, B & O R R	(C T) 9 00 A M—April 1	
Lv Chicago, C & N W R R	10 30 A M—April 1	
Ar Omaha, C & N W R R	10 30 P M—April 1	
Lv St Louis, Wabash R R	7 30 P M—March 31	
Ar Omaha, Wabash R R	8 00 A M—April 1	
Lv Kansas City, Mo Pac R R	9 00 A M—April 1	
Ar Omaha, Mo Pac R R	3 30 P M—April 1	
Lv Kansas City, C B & Q R R	12 30 P M—April 1	
Ar Omaha, C B & Q R R	6 10 P M—April 1	
Lv Minneapolis, C & N W R R	9 20 A M—April 1	
Lv St Paul, C & N W R R	9 55 A M—April 1	
Lv Rochester, C & N W R R	9 40 A M—April 1	
Lv Sioux City, C & N W R R	7 15 P M—April 1	
Ar Omaha, C & N W R R	10 00 P M—April 1	
Lv Omaha, Union Pac R R	10 30 P M—April 1	
Ar Ogden, Union Pac R R	(M T) 11 00 P M—April 2	
Lv Ogden, So Pac R R	(P T) 10 15 P M—April 2	
Ar Oakland, So Pac R R	7 00 P M—April 3	
Ar San Francisco (by ferry from Oakland)	7 30 P M—April 3	

POST-CONVENTION TOUR

Lv San Francisco, So Pac R R	11 40 P M—April 8	
Ar Merced (Yosemite Valley), So Pac R R	4 55 A M—April 9	
Note Saturday, April 9, spent in Yosemite Valley		
Lv Merced, So Pac R R	9 35 P M—April 9	
Lv Fresno, So Pac R R	11 15 P M—April 9	
Ar Los Angeles, So Pac R R	8 35 A M—April 10	
Note Los Angeles Headquarters—Los Angeles Biltmore Hotel Program of entertainment in Los Angeles, Sunday and Monday, April 10-11		
Lv Los Angeles, Santa Fe R R	12 30 P M—April 12	

Ar Grand Canyon, Santa Fe R R	8 00 A M—April 13
Note Entire day spent at Grand Canyon with headquarters at El Tovar Hotel	
Lv Grand Canyon, Santa Fe R R	7 45 P M—April 13
Ar Winslow, Santa Fe R R	7 40 A M—April 14
Note At this point members may leave the train, and visit the Petrified Forest of Arizona, rejoining the same train by motor coach at Holbrook.	
Ar Albuquerque, Santa Fe R R	4 15 P M—April 14
Ar Lamy, Santa Fe R R	6 00 P M—April 14
Note From this point is operated the Indian Detours Special one, two, or three-day motor tour to the New Mexico Rockies, visiting several Indian pueblos and ancient cliff ruins, may be arranged here	
Ar Kansas City, Santa Fe R R	5 15 P M—April 15
Note Members from Minneapolis, St Paul, Omaha, St Louis and points in the southeast will leave the party here	
Lv Kansas City, Santa Fe R R	6 15 P M—April 15
Ar Chicago, Santa Fe R R	7 20 A M—April 16
Lv Chicago, B & O R R	1 45 P M—April 16
Ar Washington, D C, B & O R R	8 40 A M—April 17
Ar Baltimore (Camden Station), B & O R R	9 43 A M—April 17
Ar Baltimore (Mt Royal Station), B & O R R	9 51 A M—April 17
Ar Wilmington, B & O R R	11 11 A M—April 17
Ar Philadelphia, B & O R R	11 44 A M—April 17
Ar New York (Jersey City Station), B & O R R	1 43 P M—April 17

Those not desiring to take the post-convention tour may return East by regular train over the same or diversified routes from San Francisco, in a period of from four to five days, depending on the route selected. They may, of course, go out with the special train and return by other routes, either railroad, steamship by way of the Panama Canal, or by air. There is a sailing over the Panama Pacific Line from Los Angeles, on April 11, arriving in New York April 25. Full details will be furnished by the Executive Secretary upon request.

Air travel by way of the United Air Lines to the convention may be arranged at the following rates, and in the time indicated:

New York to San Francisco	\$160 00	31 hours
Chicago to San Francisco	115 00	23¼ hours
Omaha to San Francisco	95 76	18½ hours
Seattle to San Francisco	43 98	7 hours
Los Angeles to San Francisco	18 95	3 hours

Similar rates from 137 cities in 30 states

THE GENERAL BUSINESS MEETING OF THE COLLEGE will be held in San Francisco on Thursday, April 7, at 4 30 P M, immediately following the general scientific program of the afternoon. All Masters and Fellows of the College are urged to be present. There will be the election of Officers, Regents and Governors, the reports of the Treasurer and the Executive Secretary, and the induction to office of the new President, Dr Francis M Pottenger, Monrovia, Calif.

THE CONVOCATION OF THE COLLEGE for the induction of newly-elected Fellows will take place Wednesday evening, April 6, at 8 00 P M, in the Gold Ballroom of the Palace Hotel.

After the induction of the new members, Dr O T Avery, of New York City, will deliver an address on "The Rôle of Specific Carbohydrates in Pneumococcus Infection and Immunity," following which he will be awarded the John Phillips Memorial Prize by the President, Dr S Marx White. After this President White will deliver the annual presidential address.

An informal reception to new members will follow immediately after the program.

THE ANNUAL BANQUET OF THE COLLEGE will be held at 7 30 o'clock, Thursday evening, April 7, at the Palace Hotel. All physicians of San Francisco and vicinity and visitors attending the Session are invited, with their ladies, by the members of the College and its Officers to attend this Banquet. A special program will be announced later. Tickets for the Banquet must be purchased at the Registration or Information Bureaus before 10 o'clock, Thursday morning.

ENTERTAINMENT FOR VISITING LADIES. A special program of entertainment for the wives, daughters and friends of attending physicians is being arranged. The ladies are most cordially invited to come to California, and to register with the Ladies' Entertainment Committee.

THE COMMERCIAL EXHIBIT will be located near the Registration Headquarters at the Palace Hotel. The Exhibit will be diversified, consisting of medical literature and texts, pharmaceutical products, apparatus and appliances, special foods, etc. These exhibits are of real scientific value, and every member should definitely arrange to inspect all of them.

FINAL PROGRAM GENERAL SESSIONS

San Francisco, Calif—April 4-8, 1932

To provide for the General Sessions a program representative of the best and most advanced work of the year has been more difficult than in some of the previous meetings. The time required for travel by some of the most distant Fellows not as yet air-minded may have proved to be occasionally a deterrent but a survey will show in spite of the difficulties a program of extraordinary breadth and wealth. One circumstance more than compensates for the distances involved for many of the Fellows and Guests. The response to invitations on the part of men in the West and on the Coast has been prompt and satisfactory. A strong and active membership in the West has been faithful and persistent in attendance wherever the College met but, naturally, has been at a numerical disadvantage in the construction of programs. To bring together a large amount of the work of this group provided an opportunity eagerly seized. The large number of new names of active workers is in line with the policies followed in constructing this program. The wealth of material submitted has made selection difficult. The program is an unusually full one.

Special attention may be called to certain features.

1 *Diseases of the kidney* receive consideration in three papers in the opening Session. These papers are practical, of the most lively interest and by men known to every student of the problem.

2 *The liver* is studied from both the experimental and practical standpoint as a part of the program on Tuesday afternoon.

3 On Tuesday evening a strong scientific program will include some of the outstanding work of the *Hooper Foundation* by its director. The work on *pulmonary tuberculosis* will include a summary of the ten years work at the Lymanhurst School for Tuberculous Children, and the relation of the paranasal sinuses to general medicine will be discussed by a long time student of this problem. The *motion picture demonstration* of the factors in the defense of the respiratory mucosa should not be missed.

4 A series of papers on Wednesday afternoon covers some very live topics on the blood vessels and, in addition to papers of practical clinical interest, includes an expo-

sition of the *physics and physiology of arteriosclerosis and hypertension* New facts about *epilepsy* are discussed and the Director of the Hooper Foundation closes the afternoon with an address on the protective measures of the State of California against *food poisoning*

5 *The endocrines* do not go unheralded Sober masters of some of their mysteries will discuss them on Thursday afternoon For this year the ever-ready heart seems crowded somewhat into the background but *circulatory failure, cardiac complications and the electrocardiogram* are found on the Thursday afternoon program

6 Symposia have been replaced for the most part by groups of papers as outlined above One symposium of outstanding significance atones for the numerical lack The Friday afternoon symposium on the *autonomic nervous system* brings together the most authoritative students of its anatomy, physiology and clinical considerations, together with a résumé of its most recent investigator, the surgeon It is planned so that the physician may have before him all of the recent great advances in knowledge of this field It is believed that this symposium alone will make attendance at this Sixteenth Annual Session worth while The Friday afternoon program closes with three papers of extraordinary interest following the symposium

The history of medicine is of interest to so large a proportion of the membership that it receives attention again in the General Session A part of the Monday evening program is given to papers by two delightful exponents of the history of our profession Medicine in Utopia and the first aphorism of Hippocrates will be treated in a manner no one would wish to miss

Those interested in the history of medicine will find opportunities in the clinic program unsurpassed at any previous session The San Francisco Committee has made special provision of papers and exhibits which should call out a large attendance These will be found in the clinic program

An intermission has been provided every afternoon except Monday On that day everyone is fresh and the varied nature of the program makes an intermission less needed In addition it has been possible to visit the exhibits during the morning and the noon hour The intermissions will be properly signalled and it is hoped that every member will respond promptly in attending the programs as they are renewed The program this year is rich and varied and it will be necessary to keep to schedule at every moment

The importance of visiting the exhibits cannot be overemphasized

OPENING GENERAL SESSION

Monday, April 4, 1932, 2 00 P M

Gold Ballroom, Palace Hotel

1 Addresses of Welcome

Robert Gordon Sproul, President of the University of California
Robert E. Swam, President of Stanford University
Langley Porter, Dean of the University of California Medical School
William Ophuls, Dean of the Stanford University Medical School
Junius B. Harris, President of the California Medical Association
Alson R. Kilgore, President of the San Francisco County Medical Society

2 Reply to Addresses of Welcome

S. Marx White,* President of the American College of Physicians

3 Pathological Differentiations in Bright's Disease

Jean Oliver, Brooklyn, N. Y.

(Guest)

4 Clinical Differentiations in Bright's Disease

Thomas Addis,* San Francisco, Calif

- 5 The Relation of Nephrosis to Nephritis
E T Bell, Minneapolis, Minn
(Guest)
- 6 Clinical Aspects of Gastric Secretion
Arthur L Bloomfield,* San Francisco, Calif
- 7 Practical Applications of Recent Discoveries in the Field of Gastro-intestinal Physiology
Walter C Alvarez,* Rochester, Minn

SECOND GENERAL SESSION

Monday Evening, April 4, 1932, 8 00 P M

Gold Ballroom, Palace Hotel

Presiding Officer

Wm J Kerr,* San Francisco, Calif

-
- 1 The Clinical Study of the Atrophic Tongue
Wm S Middleton,* Madison, Wis
 - 2 Medicine in Utopia
Richard E Scammon, Minneapolis, Minn
Dean of Medical Sciences of the University of Minnesota
(Guest)
 - 3 The First Aphorism of Hippocrates
George Dock,* Pasadena, Calif
 - 4 The Modern Hospital—Its Relationship to the Physician
B W Black, Oakland, Calif
Medical Director of the Highland Hospital of Alameda County
(Guest)

THIRD GENERAL SESSION

Tuesday Afternoon, April 5, 1932, 2 00 P M

Gold Ballroom, Palace Hotel

Presiding Officer

Walter L Bierring,* Des Moines, Ia

-
- 1 Some Aspects of Bile Function
Carl L A Schmidt, Berkeley, Calif
(Guest)
 - 2 The Effect of the Administration of Glucose and Insulin on the Glycogen Content of Normal and Experimentally Damaged Livers
T L Althausen, San Francisco, Calif
(Guest)
 - 3 Further Observations on Primary Carcinoma of the Liver in Chinese
G F Strong, Vancouver, B C
(Guest)
H H Pitts, Vancouver, B C
(Guest)
 - 4 Hepatic Pathology in Exophthalmic Goiter and the Graves Constitution
Carl V Weller,* Ann Arbor, Mich
 - 5 The Element of Error in the Diagnosis of Jaundiced Patients—A Review of 500 Cases Verified at Operation or Autopsy
George B Eusterman,* Rochester, Minn

- 6 Asthenia—Clinical Types and Principles of Therapy.
George Morris Piersol,* Philadelphia, Pa
Edward L. Bortz,* Philadelphia, Pa

INTERMISSION

Visit the Exhibits!

- 7 The Newer Aspects of Parodontosis (Pyorrhea)
Hermann Becks, San Francisco, Calif
(Guest)
- 8 The Rôle of Bacteria in Asthma
Robert L. Benson, Portland, Ore
(Guest)
- 9 Rocky Mountain Spotted Fever
G. Gill Richards,* Salt Lake City, Utah
- 10 The Significance of Fever
Hobert A. Reimann, Minneapolis, Minn
(Guest)
- 11 Poisonous Spider Bites
Emil Bogen, Olive View, Calif
(Guest)
- 12 Studies on the Chemotherapy of Amebiasis
Chauncey D. Leake, San Francisco, Calif
(Guest)

FOURTH GENERAL SESSION

Tuesday Evening, April 5, 1932, 8 00 P M

Gold Ballroom, Palace Hotel

Presiding Officer

J. C. Meakins,* Montreal, Que

- 1 Recent Studies in Equine Encephalomyelitis Discussion and Motion Picture Films
Karl F. Meyer, San Francisco, Calif
Director of the George Williams Hooper Foundation
(Guest)
- 2 Ten Years at the Lymanhurst School for Tuberculous Children
J. Arthur Myers,* Minneapolis, Minn
- 3 Treatment of Cavities in Pulmonary Tuberculosis
LeRoy S. Peters,* Albuquerque, N. M.
- 4 Atelectasis and Tuberculosis
W. Warner Watkins,* Phoenix, Ariz
H. P. Mills,* Phoenix, Ariz
Fred G. Holmes,* Phoenix, Ariz
- 5 The Paranasal Sinus Problem in the Practice of Medicine
Arthur D. Dunn,* Omaha, Nebr
- 6 Mechanical Factors in the Defense of the Respiratory Mucosa A Motion Picture
Demonstration
Anderson Hilding, Rochester, Minn
(Guest)

FIFTH GENERAL SESSION

Wednesday Afternoon, April 6, 1932, 2 00 P M

Gold Ballroom, Palace Hotel

Presiding Officer

George Morris Piersol,* Philadelphia, Pa

- 1 The Treatment of Raynaud's Disease by Repeated Exposure to Cold
Wm J Kerr,* San Francisco, Calif
- 2 Physics and Physiology of Arteriosclerosis and Hypertension
Carl J Wiggers,* Cleveland, Ohio
- 3 Aortic Hypoplasia as a Cause of Death
Edgar T Herrmann,* St Paul, Minn
- 4 Clinical Diagnosis of Pulmonary Arteriosclerosis
Henry L Ulrich,* Minneapolis, Minn
- 5 Primary (Essential) Hypertension—A Clinical and Morphological Study of Three
Hundred and Seventy-five Cases
Francis D Murphy,* Milwaukee, Wis
- 6 Hypertension—A Follow-up Study After Eight to Fifteen Years
J N Blackford,* Seattle, Wash

INTERMISSION

Visit the Exhibits!

- 7 Demonstration and Use of the Radiotherm in Disease of the Circulation
C F Tenney,* New York, N Y
- 8 Experimental Bases for Vaccine Treatment of Chronic Arthritis with Summary
of Results of Treatment
B J Clawson, Minneapolis, Minn
(Guest)
- 9 Metabolic Abnormalities in Obesity
Russell Wilder, Rochester, Minn
(Guest)
- 10 Some Recent Observations Regarding the Nature of Epilepsy
Irvine McQuarrie, Minneapolis, Minn
(Guest)
- 11 The Present Status of the Ketogenic Diet in the Treatment of Epilepsy
D Schuyler Pulford,* Woodland, Calif
- 12 The Protective Measures of the State of California Against Food Poisoning
Karl F Meyer, San Francisco, Calif
Director of the George Williams Hooper Foundation
(Guest)

Wednesday Evening, 8 00 P M

Gold Ballroom, Palace Hotel

CONVOCATION OF THE COLLEGE

The general profession and the general public are cordially invited No special admission tickets are required Evening dress is recommended

- 1 Convocation Ceremony
- 2 Address The Rôle of Specific Carbohydrates in Pneumococcus Infection and Immunity
O T Avery, New York, N Y

*F A C P

3 Presentation of the John Phillips Memorial Prize

4 Presidential Address

S Marx White, Minneapolis, Minn

Reception to New Members

An informal reception to new members will follow immediately after the Convocation exercises. Newly inducted Fellows should sign the Roster and secure their Fellowship Certificates following the Convocation program.

SIXTH GENERAL SESSION

Thursday Afternoon, April 7, 1932, 2 00 P M

Gold Ballroom, Palace Hotel

Presiding Officer

Charles G Jennings,* Detroit, Mich

1 The Biological and Clinical Importance of Ovary-Stimulating Substances

C Frederic Fluhmann, San Francisco, Calif

(Guest)

2 Animal Experiments with Adrenal Cortical Extracts

C L Connor, San Francisco, Calif

(Guest)

J L Carr, San Francisco, Calif

(Guest)

3 A Chemical Study of the Suprarenal Gland

E C Kendall, Rochester, Minn

(Guest)

4 The Clinical Syndromes of Adrenal Hyperfunction Illustrated by Lantern Slides

Hans Lissner,* San Francisco, Calif

5 Various Clinical Syndromes Associated with Diseases of the Suprarenal Glands

L R Rowntree,* Rochester, Minn

INTERMISSION

Visit the Exhibits

6 Modern Muscle Physiology and Circulatory Failure

Jonathan C Meakins,* Montreal, Que

7 The Cardiac Complications of Funnel-breast

James Gray Carr,* Evanston, Ill

8 A Study of 800 Abnormal Electrocardiograms and Associated Clinical Findings

Martin A Mortensen,* Battle Creek, Mich

The Annual General Business Meeting of the College will be held immediately after the last paper. All Masters and Fellows are urged to be present. Official reports from the Executive Secretary and Treasurer will be read, new Officers, Regents and Governors will be elected, and the President-Elect Dr Francis M Pottenger, will be inducted into office.

Thursday Evening, 7 30 P M

Palace Hotel

THE ANNUAL BANQUET OF THE COLLEGE

Toastmaster Dr Arthur L Bloomfield,* Professor of Medicine, Stanford University Medical School

Address "A Great Country Doctor"

Dr Charles J Singer, University of London, London, England

FINAL GENERAL SESSION

Friday Afternoon, April 8, 1932, 2 00 P M

Gold Ballroom, Palace Hotel

Presiding Officer

Francis M Pottenger,* Monrovia, Calif

SYMPOSIUM ON THE AUTONOMIC NERVOUS SYSTEM

- 1 Anatomy
 - a General Considerations
 - b Distribution to Skeletal Muscles and Blood Vessels

S W Ranson, Chicago, Ill
(Guest)
- 2 The Functions of the Autonomic Nervous System and Its Chemical Agents
Walter B Cannon, Boston, Mass
(Guest)
- 3 Clinical Considerations Control of Heart, Lungs and Bronchi
Harry L. Alexander, St Louis, Mo
(Guest)
- 4 Control of Blood Pressure and Renal Function
Hilding Berglund, Minneapolis, Minn
(Guest)

INTERMISSION

Visit the Exhibits!

- 5 Control of Gastro-intestinal Tract
A J Carlson,* Chicago, Ill
- 6 The Results of Sympathectomy in the Treatment of Peripheral Vascular Diseases,
Hirschsprung's Disease and Cord Bladder
Alfred W Adson, Rochester, Minn
(Guest)
- 7 Moving Picture Film "Behaviour of Animals Deprived of the Sympathetic System"
Walter B Cannon, Boston, Mass
(Guest)
- 8 Leukopenia Its Clinical Significance, with Special Reference to Aleukemic Leukemia
and Leukemoid Conditions
Stacy R Mettier,* San Francisco, Calif
- 9 The Action of Benzol, Roentgen Ray and Radium on the Blood and Blood-forming
Organs
Edwin E Osgood, Portland, Ore
(Guest)
- 10 Some Important Factors in Edema Formation
Eaton M MacKay, San Diego, Calif
(Guest)

SPECIAL CLINICS AND DEMONSTRATIONS

Clinics and demonstrations will be held in the forenoons from 9 00 to 12 00 daily,
Tuesday to Friday, inclusive

Tickets will be required for each and every one of the special clinics, ward rounds
and demonstrations The co-operation of everyone in securing his clinic tickets will
assist greatly in distributing the attendance according to the capacity of each program
It is self-evident that a ward round arranged for twenty-five will lose its value for all if

*F A C P

forty or fifty are present Ticket registration naturally is the only effective method of keeping the attendance within the capacities indicated

To all members of the College, registration blanks for the clinics and demonstrations have been distributed with the final program

A-I

Tuesday, April 5, 1932

UNIVERSITY OF CALIFORNIA HOSPITAL
(Parnassus and Third Avenues)
Toland Hall, First Floor
(Capacity—167)

- 9 00- 9 45 Mistakes in the Treatment of Heart Disease
James B Herrick, Chicago, Ill
- 9 45-10 30 Venous Pressure Determinations as Related to the Diagnosis and Treatment of Cardiac Decompensation
William S Middleton, Madison, Wis
- 10 30-11 00 Medical Clinic on Cardiovascular Diseases
William J Kerr
- 11 00-11 30 Medical Clinic on Cardiovascular Diseases
John J Sampson
- 11 30-12 00 Medical Clinic on Cardiovascular Diseases
Eugene S Kilgore

A-II

UNIVERSITY OF CALIFORNIA HOSPITAL
(Parnassus and Third Avenues)
Room 310, Third Floor
(Capacity—35)
Medical Clinic on Tuberculosis

- 9 00-10 00 Manifestations of Clinical Tuberculosis in the Adult
F M Pottenger, Monrovia, Calif
- 10 00-11 00 Juvenile Tuberculosis
Chesley Bush
- 11 00-12 00 Tuberculosis and Tuberculous Infections Among Nurses
Sidney J Shipman and Elizabeth A Davis

A-III

UNIVERSITY OF CALIFORNIA HOSPITAL
(Parnassus and Third Avenues)
Ward A, Fourth Floor
(Capacity—15)

- 9 00-10 00 Ward Rounds Cases of Cholecystitis
John M Blackford, Seattle, Wash
- 10 00-11 00 Medical Aspects
Fred H Kruse
- 11 00-12 00 Surgical Aspects
H Glenn Bell

Tuesday, April 5, 1932 (Continued)

A-IV

UNIVERSITY OF CALIFORNIA HOSPITAL
(Parnassus and Third Avenues)
Ward E, Fifth Floor
(Capacity—15)

- 9 00-10 00 Ward Rounds Gastro-intestinal Diseases
George B Eusterman, Rochester, Minn
10 00-12 00 Ward Rounds Gastro-intestinal Diseases
Elbridge J Best and Alexander G Bartlett
-

B-I

UNIVERSITY OF CALIFORNIA MEDICAL SCHOOL
Medical School Building
(Parnassus and Second Avenues)
Cole Hall, Third Floor
(Capacity—200)

- 9 00- 9 45 The Treatment of Syphilitic Aortitis
T Homer Coffen, Portland, Ore
Symposium on Syphilis
9 45-11 00 Dermatological Aspects
Howard Morrow, Hiram E Miller and Norman N Epstein.
11 00-12 00 Neurological Aspects
Edward W Twitchell
-

B-II

UNIVERSITY OF CALIFORNIA MEDICAL SCHOOL
Medical School Building
(Parnassus and Second Avenues)
Pharmacology Laboratory, Third Floor
(Capacity—50)

- 9 00- 9 30 Intravenous Magnesium Sulphate in Hypertension
H H Lissner, Los Angeles, Calif
9 30-10 00 A Study of Substitutes for Epinephrin
C H Thienes, Los Angeles, Calif
10 00-11 00 Recent Advances in Pharmacology
Chauncey D Leake
11 00-12 00 Discussion and Demonstration of Vaccines and Sera
Max S Marshall
-

B-III

UNIVERSITY OF CALIFORNIA MEDICAL SCHOOL
Medical School Building
(Parnassus and Second Avenues)
Medical Teaching Room, First Floor
(Capacity—34)

- 9 00-10 00 Lesions of the Diaphragm
J Homer Woolsey
10 00-11 00 Studies in Hemochromatosis
T L Althausen
11 00-12 00 Use of Potassium Acetate and Quinidine in Cardiac Irregularities
John B Lagen

Program of the San Francisco Meeting

Tuesday, April 5, 1932 (Continued)

B-IV

UNIVERSITY OF CALIFORNIA MEDICAL SCHOOL

Medical School Building
(Parnassus and Second Avenues)

Surgical Teaching Room, First Floor
(Capacity—20)

- 9 00-10 00 The Problem of Diabetes in Hyperthyroidism
Henry J John, Cleveland, Ohio
- 10 00-10 30 Relationship between Chronic Thyroiditis and Exophthalmic Goiter
Henry H Searls
- 10 30-11 00 Basal Rate in Toxic Adenoma
Henry H Searls
- 11 00-12 00 Malignant Goiter
Robertson Ward
-

C-I

UNIVERSITY OF CALIFORNIA MEDICAL SCHOOL

College of Dentistry Building
(Parnassus and First Avenues)

Amphitheater, Third Floor
(Capacity—168)

- 9 00-10 00 Chronic Chlorosis
Stacy R Mettler
Clinic on Hodgkin's Disease
- 10 00-11 00 Clinical Aspects
Ernest H Falconer
- 11 00-12 00 Roentgenological Aspect
Robert S Stone
-

C-II

UNIVERSITY OF CALIFORNIA MEDICAL SCHOOL

College of Dentistry Building
(Parnassus and First Avenues)

Classroom A, Third Floor
(Capacity—82)

Symposium on Hypertension

- 9 00-10 00 Arterial Hypertension
C G Jennings, Detroit, Mich
- 10 00-10 30 Clinical Aspects of Hypertension
Ernest S duBray
- 10 30-11 00 Experimental Hypertension
Dudley W Bennett
- 11 00-11 30 Eyeground Changes in Hypertension
Joseph L McCool

Tuesday, April 5, 1932 (Continued)

C-III

UNIVERSITY OF CALIFORNIA MEDICAL SCHOOL

College of Dentistry Building

(Parnassus and First Avenues)

Classroom B, Third Floor

(Capacity—40)

- 9 00-10 00 Subject to be announced
Charles J Bloom, New Orleans, La
Introduction of Communicable Diseases on Ships
- 10 00-11 00 Pneumonia, Meningitis, Ventilation
Jacob C Geiger
- 11 00-12 00 Clinical Aspects and Treatment of Communicable Diseases
Alfred C Reed
-

D-I

UNIVERSITY OF CALIFORNIA

Life Sciences Building, Berkeley

Room 2000, Second Floor

(Capacity—560)

Departments of Bacteriology and Protozoology

- 10 00-10 30 Bacterial Flora of Infected Antra
T D Beckwith and Francis M Shook
- 10 30-11 00 Human Amebiasis
C A Kofoid
- 11 00-11 15 Argasive Ticks of the Genus Ormthodorus
W B Herms
- 11 15-11 30 An Obstinate Case of Intestinal Myiasis
W B Herms
-

D-II

UNIVERSITY OF CALIFORNIA

Life Sciences Building, Berkeley

Room 2003, Second Floor

(Capacity—208)

Departments of Hygiene and Public Health

- 10 00-10 30 Statistical Pitfalls in Medical Research
Frank L Kelly and E L Lucia
- 10 30-11 00 The Relation of the Degree of Dysmenorrhea to Health Experience and
Physical Measurement
Ruby L Cunningham
- 11 00-11 30 Demonstration of the Kellogg Test for Diphtheria Immunity
Wilfred H Kellogg
-

D-III

UNIVERSITY OF CALIFORNIA

Life Sciences Building, Berkeley

Room 2503, Second Floor

(Capacity—208)

Departments of Biochemistry, Nutrition and Physiology

- 10 00-10 30 The Effect of the Calcium and Phosphorus Content of the Diet and of Vitamin
D upon Response to Parathyroid Extract Injection
A F Morgan

Tuesday, April 5, 1932 (Continued)

- 10 30-10 50 The Relation of Diffusible Calcium to Certain Diseases
David M. Greenberg
- 10 50-11 10 Some Phases of Carbohydrate Metabolism
I L Chaikoff
- 11 10-11 30 Some Phases of the Physiology of Blood Formation
Skerburne F Cook

INSTITUTE OF EXPERIMENTAL BIOLOGY

Note Demonstrations will be held by Professor Herbert M Evans and Staff in the Anatomy Department, Life Sciences Building

E-I

STANFORD UNIVERSITY MEDICAL SCHOOL

Medical School Building
(Clay and Webster Streets)
Lane Hall, Second Floor
(Capacity—333)

- 9 00-10 00 Medical Clinic on Cardiovascular Diseases
David P Barr, St. Louis, Mo
- 10 00-11 00 Medical Clinic
Arthur L Bloomfield
- 11 00-12 00 Medical Clinic
William F Cheney

E-II

STANFORD UNIVERSITY HOSPITAL

(Clay and Webster Streets)
Physiotherapy Department, Second Floor
(Capacity—15)

- 9 00-12 00 Clinic on Physical Therapeutics
H L Langnecker

E-III

STANFORD UNIVERSITY HOSPITAL

(Clay and Webster Streets)
Operating Amphitheater, Sixth Floor
(Capacity—71)

- 9 00- 9 45 Studies with the Closed Intestinal Loop
George E Burget, Portland, Ore
- 9 45-10 30 Treatment of Stenosis of the Esophagus
John H Fitzgibbon, Portland, Ore
- 10 30-11 00 Anesthesia from the Internist's Standpoint.
Caroline B Palmer and Staff
- 11 00-11 30 Whole Blood Transfusion, Demonstration of Technique
LeRoy Brooks
- 11 30-12 00 Bone Tumors A General Practice Problem
Merrill Mensor.

E-IV

STANFORD UNIVERSITY HOSPITAL

Children's Ward, Fourth Floor
(No Program on Tuesday)

Tuesday, April 5, 1932 (Continued)

E-V

STANFORD UNIVERSITY MEDICAL SCHOOL

Medical School Building
(Clay and Webster Streets)
Room 311, Third Floor
(Capacity—112)

- 9 00- 9 15 The Use of Dessicated Posterior Pituitary in a Case of Diabetes Insipidus
Harold B Myers, Portland, Ore
- 9 15- 9 30 The Pathology of Hyperthyroidism
Frank R Menne, Portland, Ore
- 9 30-10 15 Ovary-Stimulating Substances in the Blood of Women
C Frederic Fluhmann
- 10 15-11 00 Addison's Disease with Tumors of Suprarenals
Donald A Carson
- 11 00-11 30 Results after Total Thyroidectomy
Willard E Kay and Philip K Gilman
- 11 30-12 00 Experimental Hypophysectomy
Frederick L Reichert

F-I

STANFORD UNIVERSITY MEDICAL SCHOOL

Nurses' Home
(2340 Clay Street)
Assembly Room, First Floor
(Capacity—280)

- 9 00- 9 45 Generalized Tuberculosis
Allen K Krause, Tucson, Ariz
- 9 45 10 30 Treatment of Pulmonary Cavities
Charles W Mills, Tucson, Ariz
- 10 30-11 00 A Study of the Bronchial, Pulmonary and Lymphatic Circulation of the
Lungs under Various Pathological Conditions, Experimentally Pro-
duced
Emile F Holman
- 11 00-11 30 A Discussion of the Relationship of Upper Respiratory Infection to Acute
and Chronic Tuberculous and Pyogenic Pulmonary Disease
Philip H Pierson
- 11 30-12 00 Infection of Accessory Nasal Sinuses as a Factor in Diseases of the Lungs
Samuel H Hurwitz and Edward C Sewall

F-II

STANFORD UNIVERSITY MEDICAL SCHOOL

Nurses' Home
(2340 Clay Street)
Room 5, First Floor
(Capacity—74)

- 9 00- 9 30 (Subject to be announced later)
Sydney R Miller, Baltimore, Md
- 9 30-10 00 Demonstration of Coccidioidal Granuloma
Ernest Dickson and Staff
- 10 00-10 30 Remarks on Bone Marrow Biopsy Studies
Harry A Wyckoff and Loren R Chandler

Tuesday, April 5, 1932 (Continued)

- 10 30-11 00 Studies in the Behavior of a Benign Transplantable Tumor
Ludwig A Emge.
- 11 00-11 20 Diuretics and the Mechanism of Diuresis
Andrew B Stockton
- 11 20-11 40 Experimental Studies of Epinephrine Substitutes
Maurice L Tainter
- 11 40-12 00 Protective Action of Colloidal Dyes in Intoxication
Paul J Hanzlik
-

F-III

STANFORD UNIVERSITY MEDICAL SCHOOL

Nurses' Home
(2340 Clay Street)
Room 4, First Floor
(Capacity—80)

- 9 00- 9 30 The Heart in Hypothyroidism
Homer Rush, Portland, Ore
- 9 30-10 00 The Three Common Types of Blood Pressure in Vascular Disease
Willard J Stone, Pasadena, Calif
- 10 00-10 30 Anomalies of the Great Vessels of the Chest
William Dock
- 10 30-11 00 Graphic Records of Gallop Rhythm
J K Lewis
- 11 00-11 20 Prediction and Measurement of the Cardiac Silhouette
Robert R Newell
- 11 20-11 40 Circulatory Changes in the Fundus Oculi
Hans Barkan
- 11 40-12 00 Pitfalls in the Diagnosis of Hydrothorax in Cardiac Decompensation
Wm W Newman
-

G

STANFORD UNIVERSITY MEDICAL SCHOOL

Preclinical Departments, Palo Alto
(No Program on Tuesday)

H-I

SAN FRANCISCO HOSPITAL

(22nd Street and Potrero Avenue)
University of California Service
Ward E, First Floor
(Capacity—20)

- 9 00-10 00 Ward Rounds (Ward E, First Floor)
LeRoy H Briggs and Staff
- 10 00-11 00 Ward Rounds Cardiovascular Diseases (Ward H, Fourth Floor)
George Morris Piersol, Philadelphia, Pa

Tuesday, April 5, 1932 (Continued)

H-II

SAN FRANCISCO HOSPITAL
(22nd Street and Potrero Avenue)
University of California Service
Amphitheater, Third Floor
(Capacity—100)

- 9 00-11 00 Symposium on Pulmonary Tuberculosis
Harold Brunn, A Lincoln Brown and Esther Rosencrantz
11 00-12 00 Medical X-Ray Conference
Lloyd Bryan and the Medical and Surgical Staffs

H-III

SAN FRANCISCO HOSPITAL
(22nd Street and Potrero Avenue)
University of California Service
Council Room, First Floor
(Capacity—35)

- 9 00-10 00 Differential Diagnosis of Bronchogenic Carcinoma
Marr Bisailon, Portland, Ore
10 00-10 15 Exhibition of Anatomical Drawings
Curle L. Callander
10 15-10 45 Exhibition of 350 Gall Stones Discussion of Their Etiology
Stanley Mentzer
10 45-11 00 Motion Picture of Operation of Pulmonary Embolectomy
A Lincoln Brown
11 00-12 00 Recognition of Intestinal Obstruction and Some Aspects of Gastro-intestinal Surgery
George K Rhodes

H-IV

SAN FRANCISCO HOSPITAL
(22nd Street and Potrero Avenue)
University of California Service
Ward 30, Fifth Floor
(Capacity—20)

- 9 00-10 30 Pediatric Clinic Endocrine Disorders
Orville Barbour, Peoria Ill, and Wm Anthony Reilly
10 30-12 00 Ward Rounds Tuberculosis in Infants with Special Reference to Prognosis
William Anthony Reilly

H-V

SAN FRANCISCO HOSPITAL
(22nd Street and Potrero Avenue)
University of California Service
Ward C Office, Third Floor
(Capacity—10)

- 9 00-11 00 Demonstration of Eyegrounds
Warren D Horner

Tuesday, April 5, 1932 (Continued)

I

CHILDREN'S HOSPITAL

(3700 California Street)

Nurses' Home

Recreation Hall, Annex, First Floor

(Capacity—100)

- 9 00- 9 40 Allergy in Infancy and Childhood
George Piness, Los Angeles, Calif
- 9 40-10 10 Presentation of Allergic Cases
J M Bierman and H E Thelander
- 10 10-10 40 Rheumatic Endocarditis Presentation of Cases
Ann Purdy
- 10 40-11 00 Tremendous Enlargements of the Left Auricle in a Patient with Long-standing Mitral Stenosis, Auricular Fibrillation and Adhesive Pericarditis, Report of a Case
E Richmond Ware, Los Angeles, Calif
- 11 00-11 30 Blood Pictures of Healthy Infants
Clair F Gelston
- 11 30-12 00 Presentation of Cases
Myrl M Morris

J

FRANKLIN HOSPITAL

(14th and Noe Streets)

(No Program on Tuesday)

K

FRENCH HOSPITAL

(Geary Street and 5th Avenue)

Auditorium, First Floor

(Capacity—250)

- 9 00- 9 45 Clinic on Postoperative Pulmonary Complications
Maurice C Pincoffs, Baltimore, Md
- 9 45-10 30 Visualization of Gall Bladder by Plain Film
Lloyd B Crow.
- 10 30-11 15 Diagnosis and Localization of Tumors of the Brain
E B Towne
- 11 15-12 00 Acute Contraction of Muscles Due to Trauma and Excessive Venous Hemorrhage in Closed Fractures of the Extremities
Ethan H Smith

L

LAGUNA HONDA HOME

(7th Avenue and Dewey Blvd)

(No Program on Tuesday)

M

LETTERMAN GENERAL HOSPITAL

United States Presidio

(No Program on Tuesday)

Tuesday, April 5, 1932 (Continued)

N

MARINE HOSPITAL
(14th Avenue and Lake Street)
(No Program on Tuesday)

O

MARY'S HELP HOSPITAL
(145 Guerrero Street)
(No Program on Tuesday)

P-I

MOUNT ZION HOSPITAL
Nursing School Auditorium, First Floor
(2345 Sutter Street)
(Capacity—300)

- 9 00- 9 30 Diagnosis of Organic Diseases of the Nervous System
Samuel D Ingham, Los Angeles, Calif
- 9 30-10 00 A Few Interesting Neurological Experiences
W F Beerman
- 10 00-10 30 Myasthenia Gravis
Mervyn H Hirschfeld
- 10 30-11 00 Cultivation of Anterior Poliomyelitis Virus
Frederick Eberson
- 11 00-11 30 Physiology of Dreams
E O Jellinek
- 11 30-12 00 Thrombosis of the Anterior Spinal Artery
Julian M Wolfsohn

P-II

MOUNT ZION HOSPITAL
Nursing School Classroom, First Floor
(No Program on Tuesday)

Q

ST FRANCIS HOSPITAL
(Hyde and Bush Streets)
(No Program on Tuesday)

R

ST JOSEPH'S HOSPITAL
(Park Hill and Buena Vista Avenues)
(No Program on Tuesday)

S

ST LUKE'S HOSPITAL
(27th and Valencia Streets)
(No Program on Tuesday)

Tuesday, April 5, 1932 (Continued)

T-I

ST MARY'S HOSPITAL
(Hayes and Stanyan Streets)
Auditorium, Second Floor
(Capacity—400)

- 9 00- 9 45 A Clinical Review of Pulmonary Infection
Donald J Frick, Los Angeles, Calif
- 9 45-10 30 Aortic Hypoplasia
Edgar T Herrmann, St Paul Minn
- 10 30-11 15 Carbon Dioxide in the Treatment of Bronchopneumonia of Children.
Randolph G Flood
- 11 15-12 00 Systolic Murmurs Their Significance Evaluated by Fluoroscopic Examination
of the Left Auricle in Oblique Position Moving Pictures
Harry Spiro

T-II

ST MARY'S HOSPITAL
(Hayes and Stanyan Streets)
Lecture Room No 1, First Floor
(Capacity—75)

- 9 00-10 00 The Relationship of the Internist to the Surgeon in the Handling of Surgical
Diabetes
Leander A Riely, Oklahoma City, Okla
- 10 00-11 00 Chylothorax
Thomas J Lennon
- 11 00-12 00 Presentation of Selected Dermatological Cases
Harry E Alderson

T-III

ST MARY'S HOSPITAL
(Hayes and Stanyan Streets)
Lecture Room No 2, Third Floor
(Capacity—50)

- 9 00-10 30 Muscular Dystrophies Presentation of Cases
Milton B Lennon
- 10 30-12 00 Scope and Field of the Private Hospital Laboratory
Elmer W Smith

U

SHRINERS HOSPITAL FOR CRIPPLED CHILDREN
(19th Avenue and Moraga Street)
Clinic Waiting Room, First Floor
(Capacity—75)

- 9 00-10 00 Ward Rounds
S L Haas
- 10 00-12 00 Presentation of Cases
S L Haas
- a Results of Muscle Transplantation in Paralysis Following Anterior
Poliomyelitis
- b Operative Treatment for Tuberculosis of the Hip
- c Results after Reduction of Congenital Dislocation of the Hip Joint

Tuesday, April 5, 1932 (Continued)

V

SOUTHERN PACIFIC HOSPITAL
(Fell and Baker Streets)
Auditorium, Fifth Floor
(Capacity—125)

- 9 00-10 00 The Recognition and Management of Cardiac Pain
Louis F Bishop and Louis F Bishop, Jr, New York, N Y
- 10 00-10 30 Some Etiological Factors in Precordial Pain
Bernard Kaufman
- 10 30-11 30 The Justification for the Diagnosis of Angina Pectoris
Philip K. Brown
- 11 00-12 00 Cervical Sympathectomy
a Dissections of the Cervical Sympathetic
John D Humber
b Operative Results with Demonstration of Cases
Walter B Coffey

W

SAN FRANCISCO COUNTY MEDICAL SOCIETY BUILDING
(2180 Washington Street)
Meeting Room
(Capacity—100)

Early History of Medicine on the Pacific Coast

- 9 00- 9 45 Mexico
Nathan Van Patten
- 9 45-10 30 Peru
Jay Randolph Sharpsteen
- 10 30-11 15 California
Henry Harris
- 11 15-12 00 Pacific Northwest
Olof Larsell

Wednesday, April 6, 1932

A-I

UNIVERSITY OF CALIFORNIA HOSPITAL
(Parnassus and Third Avenues)
Toland Hall, First Floor
(Capacity—167)

- 9 00- 9 30 Clinical Studies on the Treatment of Amebiasis with Carbarsone
William M James, Panama, R P, Hamilton H Anderson and Dorothy Koch
- 9 30-12 00 Clinic on Amebiasis
Ernest L. Walker, Alfred C Reed and Chauncey D Leake

A-II

UNIVERSITY OF CALIFORNIA HOSPITAL
(Parnassus and Third Avenues)
Room 310, Third Floor
(Capacity—35)

- 9 00- 9 45 Hemochromatosis, Subacute Yellow Atrophy of the Liver and Iron Retention.
Adolph Sachs, Omaha, Nebr

Wednesday, April 6, 1932 (Continued)

- 9 45-10 00 Studies on Cirrhosis of the Liver
Frank R Menne, Portland, Ore
- 10 00-11 00 Cirrhosis of the Liver
Fred H Kruse and T J Althausen
- 11 00-12 00 Serum Proteins in the Malnourished
Frederick Bruckman

A-III

UNIVERSITY OF CALIFORNIA HOSPITAL
(Parnassus and Third Avenues)
Ward A, Fourth Floor
(Capacity—15)

- 9 00 10 00 Ward Rounds Cardiovascular Diseases
George Dock, Pasadena, Calif.
- 10 00-11 00 Ward Rounds
Harry L Alexander, St Louis, Mo
- 11 00-12 00 Ward Rounds
Herbert W Allen

A-IV

UNIVERSITY OF CALIFORNIA HOSPITAL
(Parnassus and Third Avenues)
Ward E, Fifth Floor
(Capacity—15)

- 9 00-10 00 Ward Rounds The Heart in Pregnancy
S Marx White, Minneapolis, Minn
- 10 00-11 00 Ward Rounds Heart Disease before and after Middle Life
George E Ebricht
- 11 00-12 00 Ward Rounds
Felix Cunha

B-I

UNIVERSITY OF CALIFORNIA MEDICAL SCHOOL
Medical School Building
(Parnassus and Second Avenues)
Cole Hall, Third Floor
(Capacity—200)

- 9 00- 9 30 1 Some Organizations of Questionable Etiological Significance Isolated
from Stools and Urine Submitted for Examination for Members of
the Typhoid-Paratyphoid-Dysentery Group
- 2 The Nature of the Slow-Lactose-Fermenting B. Coh Found in
Stools and Urine
Harry J Sears, Portland, Ore
The Problem of Undulant Fever in the West
- 9 30-11 00 Etiology and Epidemiology
Karl F Meyer
- 11 00-12 00 Clinical Types Presentation of Cases
William J Kerr

Wednesday, April 6, 1932 (Continued)

B-II

UNIVERSITY OF CALIFORNIA MEDICAL SCHOOL

Medical School Building
(Parnassus and Second Avenues)
Pharmacology Laboratory, Third Floor
(Capacity—50)

- 9 00-12 00 Clinico-Pathological Conference Endocrine Disorders
L G Rowntree, Rochester, Minn, H Lissner, Frank Hinman, Howard
W Fleming and Charles L Connor
-

B-III

UNIVERSITY OF CALIFORNIA MEDICAL SCHOOL

Medical School Building
(Parnassus and Second Avenues)
Medical Teaching Room, First Floor
(Capacity—34)

- 9 00-10 30 Clinic on Allergy in Infancy and Childhood
George Piness, Los Angeles, Calif, Francis S Smith and Minnola Stallings
10 30-11 00 Intestinal Allergy
Albert H Rowe
11 00-11 30 The Role of Bacteria in Allergy
Robert L Benson, Portland, Ore
11 30-12 00 Medical Clinic on Allergy
Irwin C Schumacher
-

B-IV

UNIVERSITY OF CALIFORNIA MEDICAL SCHOOL

Medical School Building
Surgical Teaching Room, First Floor
(Capacity—20)

- 9 00-10 00 The Problems Relating to the Use of Thallium in Rodent Control
Tracy I Storer, Davis, Calif
10 00-12 00 Experiences in the Recent Outbreak of Thallium Poisoning in California—
Clinical Features
H M Ginsburg, Fresno, Calif
Pathological Studies on Fatal Cases
C E Nixon, Fresno, Calif
-

C-I

UNIVERSITY OF CALIFORNIA MEDICAL SCHOOL

College of Dentistry Building
(Parnassus and First Avenues)
Amphitheater, First Floor
(Capacity—168)

- 9 00- 9 45 The Etiology and Treatment of Abscess of the Lung
James Alex Miller, New York, N Y
9 45-10 15 Pulmonary Suppuration Medical Aspects
Sidney J Shipman

Wednesday, April 6, 1932 (Continued)

- 10 15-11 15 Pulmonary Suppuration Surgical Aspects
Harold Brunn
- 11 15-11 30 Etiology of Pulmonary Emphysema
M Prinzmetal
- 11 30-12 00 Postoperative Pulmonary Atelectasis
William B Faulkner, Jr

C-II

UNIVERSITY OF CALIFORNIA MEDICAL SCHOOL
College of Dentistry Building
(Parnassus and First Avenues)
Classroom A, Third Floor
(Capacity—82)

- 9 00-10 00 Vaccine Treatment of Chronic Arthritis
B J Clawson, Minneapolis, Minn
Clinics on Backache
- 10 00-10 30 Orthopedic Clinic
LeRoy Abbott
- 10 30-11 00 Medical Clinic
William L Bender
- 11 00-11 30 Gynecological Clinic
Alice F Maxwell
- 11 30-12 00 Neurological Clinic
Richard W Harvey

C-III

UNIVERSITY OF CALIFORNIA MEDICAL SCHOOL
College of Dentistry Building
(Parnassus and First Avenues)
Classroom B, Third Floor
(Capacity—40)

- 9 00- 9 45 Demonstration Clinic on Polycythemia
Charles T Stone, Galveston, Texas
Medical Clinic on Leukemia
- 9 45-10 30 Cell Morphology
James F Rinehart
- 10 30-11 15 Clinical Aspects
Stacy R Mettner
- 11 15-12 00 Leukemoid Blood States Cases
Ernest H Falconer and Alfred H Heald

D

UNIVERSITY OF CALIFORNIA
Preclinical Departments, Medical School
Life Sciences Building, Berkeley
(No program on Wednesday)

Wednesday, April 6, 1932 (Continued)

E-I

STANFORD UNIVERSITY MEDICAL SCHOOL
Medical School Building
(Clay and Webster Streets)
Lane Hall, Second Floor
(No program on Wednesday)

E-II

STANFORD UNIVERSITY HOSPITAL
(Clay and Webster Streets)
Physiotherapy Department, Second Floor
(No program on Wednesday)

E-III

STANFORD UNIVERSITY HOSPITAL
Operating Amphitheater, Sixth Floor
(No program on Wednesday)

E-IV

STANFORD UNIVERSITY HOSPITAL
(Clay and Webster Streets)
Children's Ward, Fourth Floor
(Capacity—15)

9 00-12 00 Pediatric Ward Rounds Demonstration of Cases and Discussion of Special
Topics
Harold K. Faber and Staff

E-V

• STANFORD UNIVERSITY MEDICAL SCHOOL
Medical School Building
Room 311, Third Floor
(No program on Wednesday)

F-I

STANFORD UNIVERSITY MEDICAL SCHOOL
Nurses' Home
(2340 Clay Street)
Assembly Room, First Floor
(Capacity—280)

9 00- 9 15 Pathological Differentiation in Bright's Disease
Jean R. Oliver, Brooklyn, N. Y.

9 15 -9 45 Clinic on Diuretics
Burrell O. Raulston, Los Angeles, Calif.

9 45-10 30 Clinic on Bright's Disease
Thomas Addis

10 30-11 00 Physiological Reaction of Insulin
Dwight E. Shepardson

11 00-11 30 A High Fat Modification of Joslin's Diabetic Card
Horace Gray and Jean Stewart

11 30-12 00 Disorders of Growths, Illustrated with Lantern Slides
Horace Gray and L. M. Bayer

Wednesday, April 6, 1932 (Continued)

F-II

STANFORD UNIVERSITY MEDICAL SCHOOL

Nurses' Home
(2340 Clay Street)
Room 5, First Floor
(Capacity—74)

- 9 00- 9 30 Gastro-intestinal Diseases
Walter C Alvarez, Rochester, Minn.
- 9 30-10 00 Cholecystography
Edward Leef
- 10 00-10 30 Clinical and Pathological Demonstrations
Gunther W Nagel
- 10 30-11 00 Diagnosis of Amebiasis
Herbert Gunn
- 11 00-11 30 Jaundice
Donald A Carson
- 11 30-12 00 Indigestion and Related Problems
Arthur L Bloomfield and Associates

F-III

STANFORD UNIVERSITY MEDICAL SCHOOL

Nurses' Home
(2340 Clay Street)
Room 4, First Floor
(Capacity—80)

- 9 00- 9 30 Occlusive and Vasomotor Diseases Affecting the Extremities
George E Brown, Rochester, Minn
- 9 30-10 00 Demonstration of Patients
Walter F Schaller and Thomas G Inman
- 10 00-10 30 The 1931 Polyneuritis Demonstration of Patients
Julian M Wolfsohn
- 10 30-11 00 Clinical Studies in Epilepsy
Helen Hopkins-Detrick
- 11 00-11 20 Study of Variations in the Roentgenological Appearance of Cerebral Arteries
Melvin Somers
- 11 20-11 40 Anionic Bismuth Therapy in Neurosyphilis
Henry G Mehrtens and Pearl S Pouppirt
- 11 40-12 00 Typical and Atypical Cranial Neuralgias
Frederick L Reichert

G

STANFORD UNIVERSITY MEDICAL SCHOOL

Preclinical Departments, Palo Alto
Departments of Anatomy and Physiology
Anatomy Lecture Room
(Capacity—80)

- 10 00-10 45 The Present Status of the Poliomyelitis Problems Motion Picture of Experimental Poliomyelitis
E W Schultz
Room 460, Department of Physiology

Wednesday, April 6, 1932 (Continued)

- 10 45-11 00 Demonstration of the Effect of Some Brain Lesions on Behavior
Victor Hall
Room 460, Department of Physiology
- 11 00-11 30 The Effects of Protein Diet
J R Slonaker

H

SAN FRANCISCO HOSPITAL
(22nd Street and Potrero Avenue)
Stanford University Service
Medical Amphitheater, Third Floor, Operating Pavilion
(Capacity—105)

- 9 00- 9 45 Some Types of Blood Dyscrasia
John H Musser, New Orleans, La
- 9 45-10 30 Treatment of Addisonian Anemia with Digested Beef
Garnett Cheney
- 10 30-11 15 Skin Reactions to the Application of Ice
George D Barnett
- 11 15-12 00 Jacksonian Epilepsy
Julian M Wolfsohn

I

CHILDREN'S HOSPITAL
(3700 California Street)
(No Program on Wednesday)

J

FRANKLIN HOSPITAL
(14th and Noe Streets)
(No Program on Wednesday)

K-I

FRENCH HOSPITAL
(Geary Street and 5th Avenue)
Auditorium, First Floor
(Capacity—250)

- 9 00-10 00 Clinic on Peptic Ulcer
Clement R Jones, Pittsburgh, Pa
- 10 00-10 30 Peptic Ulcer
Philip K Brown
- 10 30-11 00 Surgical Aspects of Peptic Ulcer
John W Cline
- 11 00-11 30 Indications for Surgical Intervention in Peptic and Duodenal Ulcers
Asa W Collins
- 11 30-12 00 Surgical Emergencies of Peptic Ulcers
W W Washburn

Program of the San Francisco Meeting

K-II

Wednesday, April 6, 1932 (Continued)

FRENCH HOSPITAL
(Gear y Street and 5th Avenue)
Outpatient Department
(Capacity—50)

9 00-12 00 Clinical Demonstration of Unusual Dermatological Cases
E D Chipman and Jay Jacobs

L

LAGUNA HONDA HOME
(7th Avenue and Dewey Blvd)
University of California Service
Sun Room, Ward 4, First Floor
(Capacity—50)

9 00- 9 45 A Comparison of the Treatment of Auricular Fibrillation with Whole Leaf
and Glucoside Digitalis
William D Stroud, Philadelphia, Pa
9 45-10 30 The Place of the Chronic Hospital in the Community, with Particular
reference to the Care and Study of So-Called Degenerative Disease
Ernest S duBray
10 30-11 15 Coccidioides of the Skin
Norman N Epstein
11 15-12 00 Tuberculosis and Ano-Rectal Fistulae
Montague S Woolf

M-I

LETTERMAN GENERAL HOSPITAL
(United States Presidio)
Assembly Hall
(Capacity—100)

9 00-10 00 Clinic on Bright's Disease
Francis D Murphy, Milwaukee, Wis
10 00-11 00 The Common Types of Heart Disease, with Presentation of Ca
Major W C Munly, M C
11 00-12 00 The Natural History of the Common Types of Heart Disease
Major W C Munly, M C

M-II

LETTERMAN GENERAL HOSPITAL
(United States Presidio)
Ward S-1
(Capacity—60)

9 00-10 30 Selected Neurological Cases
Lt Col T D Woodson, M C
10 30-12 00 Neurosyphilis Presentation of Cases
Major W D Mueller, M C

Wednesday, April 6, 1932 (Continued)

M-III

LETTERMAN GENERAL HOSPITAL
(United States Presidio)
Ward O-1
(Capacity—15)

- 9 00-10 30 Peptic Ulcer with Presentation of Cases
Major D B Faust, M C
- 10 30-12 00 Malignant Disease of the Colon Its Diagnosis and Technique of Proctoscopy (X-Ray Clinic Building)
Major D B Faust, M C
-

N

MARINE HOSPITAL
(14th Avenue and Lake Street)
(No Program on Wednesday)

O

MARY'S HELP HOSPITAL
(145 Guerrero Street)
(No Program on Wednesday)

P-I

MOUNT ZION HOSPITAL
(2345 Sutter Street)
Nursing School Auditorium, First Floor
(Capacity—300)

- 9 00-10 00 Demonstration Clinic Gastro-intestinal Diseases
Elmer L Eggleston, Battle Creek, Mich
- 10 00-10 30 Hemorrhage of the Upper Intestinal Tract
Adolph N Nahman
- 10 30-11 00 The Irritable Colon
Allan L Cohn
- 11 00-11 30 Malignant Lymphoma
LeRoy H Briggs
- 11 30-12 00 Pathology of Malignant Lymphoma
Glanville Y Rusk
-

P-II

MOUNT ZION HOSPITAL
(2345 Sutter Street)
Nursing School Classroom, First Floor
(Capacity—47)

- 9 00- 9 30 Changes in Mitochondria Induced by Alterations in the Glucose-Glycogen Equilibrium
E M Hall, Los Angeles Calif, and E M MacKay, La Jolla, Calif
- 9 30-10 15 Modification of Blood Chemistry Tests
William G Mossman
- 10 15-11 00 Hinton Test for Syphilis
Edgar J Munter
- 11 00-11 30 Tuberculin Ointment Adhesive Tape Test
Ernst Wolff
- 11 30-12 00 Blood Serum Colloidal Gold Tests in Poliomyelitis Susceptibility
Frederick Ebersson

Wednesday, April 6, 1932 (Continued)

Q

ST. FRANCIS HOSPITAL

(1190 Bush Street)

Nurses' Lecture Room, Basement

(Capacity—60)

- 9 00- 9 30 Analysis of Blood Serum with Newer Methods
Paul B Roen, Hollywood, Calif
- 9 30- 9 50 Etiology of Duodenal Ulcer
Emmet Allen
- 9 50-10 10 Anomalies of the Gastro-intestinal Tract
James A Guilfoil
- 10 10-10 30 Duodenal Adhesions in Relation to Pathological Gall Bladder
C A. Fogerty
- 10 30-11 00 Treatment of Pulmonary Tuberculosis by Extra-pleural Paraffin Filling.
Cabot Brown
- 11 00-11 30 Therapeutic Problems in Bronchial Asthma
Edward Matzger
- 11 30-12 00 Paranoiac Trends in Women in the Presenile Period
Edward W Twitchell

R

ST JOSEPH'S HOSPITAL

(Park Hill and Buena Vista Avenues)

Social Hall, Basement

(Capacity—60)

- 9 00-10 00 Oxygen in Coronary Heart Disease
Robert I. Rizer, Minneapolis, Minn
- 10 10-11 00 Coronary Thrombosis
Walter L. Bierring, Des Moines, Iowa
- 11 00-12 00 Coronary Thrombosis.
Eugene S Kilgore

S-I

ST LUKE'S HOSPITAL

(27th and Valencia Streets)

Clinic Building, Top Floor

(Capacity—50)

- 9 00-10 00 Ward Rounds
James H Means, Boston, Mass
- 10 00-11 00 Usual and Unusual Agranulocytic Pictures
Harold P Hill

S-II

ST LUKE'S HOSPITAL

(27th and Valencia Streets)

Pope Ward, Basement

(Capacity—50)

- 10 00-12 00 Ward Rounds - Pediatrics
George D Lym

Wednesday, April 6, 1932 (Continued)

S-III

ST LUKE'S HOSPITAL
(27th and Valencia Streets)
X-Ray Department, Basement
(Capacity—25)

- 9 00-12 00 Radiographic Demonstration
Howard E Ruggles and Charles D Fulmer

S-IV

ST LUKE'S HOSPITAL
(27th and Valencia Streets)
Clinical Laboratory, Third Floor
(Capacity—25)

- 9 00-12 00 Clinical Laboratory Demonstration
W Parker Stowe and G D Delprat

T-I

ST MARY'S HOSPITAL
(Hayes and Stanyan Streets)
Auditorium, Second Floor
(Capacity—400)

- 9 00-10 00 Treatment of Stenosis of the Esophagus
John H Fitzgibbon, Portland, Ore
10 00-11 00 Congenital Abdominal Bands A Roentgenological and Clinical Review
John R O'Neill
11 00-12 00 Abnormal Physiology of the Gastro-intestinal Tract
James A Guilfoil

T-II

ST MARY'S HOSPITAL
(Hayes and Stanyan Streets)
Lecture Room No 1, Third Floor
(Capacity—75)

- 9 00- 9 45 Moving Picture Film Demonstrating the Effects of Various Irregularities on
Dogs' Hearts
Carl J Wiggers, Cleveland, Ohio
9 45-10 00 Tremendous Enlargement of the Left Auricle in a Patient with Long-
Standing Mitral Stenosis, Auricular Fibrillation and Adhesive Peri-
carditis Report of a Case
E Richmond Ware, Los Angeles, Calif
10 00-10 45 Arteriosclerosis and Diabetes
Anthony Diepenbrock
10 45-11 30 Cardiac Irregularities, Illustrated by Moving Pictures on Living Animals
Harry Spiro

T-III

ST MARY'S HOSPITAL
(Hayes and Stanyan Streets)
Lecture Room No 2, Third Floor
(No Program on Wednesday)

Wednesday, April 6, 1932 (Continued)

T-IV

ST MARY'S HOSPITAL
(Hayes and Stanyan Streets)
Children's Ward, Fourth Floor
(Capacity—50)

- 9 00- 9 30 Intelligence Rating in Juvenile Diabetes
Howard F West, Los Angeles, Calif
9 30-11 30 Pediatric Ward Rounds
Randolph G Flood
11 30-12 00 Radium Treatment Presentation of Cases
Monica Donovan
-

U

SHRINERS HOSPITAL FOR CRIPPLED CHILDREN
(19th Avenue and Moraga Street)
(No Program on Wednesday)

V

SOUTHERN PACIFIC HOSPITAL
(Fell and Baker Streets)
(No Program on Wednesday)

W

HISTORICAL PROGRAM
(No Program on Wednesday)

Thursday, April 7, 1932

A-I

UNIVERSITY OF CALIFORNIA HOSPITAL
(Parnassus and Third Avenues)
Toland Hall, First Floor
(Capacity—167)

- 9 00-10 00 Evaluation of Insulin After Ten Years
Russell Wilder, Rochester, Minn
10 00-11 00 Results of Ten Years' Experience in the Use of Insulin
Jonathan Meakins, Montreal, Can
11 00-11 30 Diabetic Coma The Use of Insulin in Treatment
H Clare Shepardson
11 30-11 45 Coronary Disease in Diabetes
Howard W West, Los Angeles, Calif
11 45-12 00 Relation of Glycogen Formation to Ketosis
H J Deuel, Los Angeles, Calif
-

A-II

UNIVERSITY OF CALIFORNIA HOSPITAL
(Parnassus and Third Avenues)
Room 310, Third Floor
(Capacity—35)

- 9 00-10 00 Clinic on Epilepsy
Irvine McQuarrie, Minneapolis, Minn
10 00-12 00 Metabolic Studies in Children
Francis S Smyth and Staff

Thursday, April 7, 1932 (Continued)

*A-III*UNIVERSITY OF CALIFORNIA HOSPITAL
(Parnassus and Third Avenues)
Ward A, Fourth Floor
(Capacity—15)

- 9 00-10 00 Ward Rounds Vasomotor Diseases Affecting the Extremities
George E. Brown, Rochester, Minn
- 10 00-11 00 Ward Rounds Circulatory Diseases of the Extremities
William J. Kerr
- 11 00-12 00 Ward Rounds Diseases of the Spleen
S. P. Lucia
-

*A-IV*UNIVERSITY OF CALIFORNIA HOSPITAL
(Parnassus and Third Avenues)
Ward E, Fifth Floor
(Capacity—15)

- 9 00-10 30 Ward Rounds Diseases of the Ductless Glands
James H. Means, Boston, Mass
- 10 30-12 00 Ward Rounds Diseases of the Ductless Glands
H. Lissner
-

*BI*UNIVERSITY OF CALIFORNIA MEDICAL SCHOOL
Medical School Building
(Parnassus and Second Avenues)
Cole Hall, Third Floor
(Capacity—200)

- 9 00- 9 30 Studies of the Effect of Feeding Various Types of Thyroid Tissues on
Hearts of Rabbits
Frank R. Menne, Portland, Ore
- 9 30-10 00 Experimental and Clinical Observations on the Pathology and Treatment
of Exophthalmos
Howard C. Naffziger
- 10 00-10 30 Histogenesis of Neuroglia and Oligodendroglia
Ottiswell W. Jones
- 10 30-12 00 Neurosurgical Clinic
Howard C. Naffziger and Staff
-

*B-II*UNIVERSITY OF CALIFORNIA MEDICAL SCHOOL
Medical School Building
(Parnassus and Second Avenues)
Pharmacology Laboratory, Third Floor
(Capacity—50)

- 9 00- 9 15 An Experimental Study of Cinchophen Hepatitis
Harold B. Myers, Portland, Ore
- 9 15-10 15 Recent Advances in Pharmacology
Chauncey D. Leake
- 10 15-11 00 Discussion and Demonstration of Vaccines and Sera
Max S. Marshall

Thursday, April 7, 1932 (Continued)

- 11 00-11 30 Treatment of Typhoid Fever with Bacteriophage
Thos C. McCleave, Berkeley, Calif
- 11 30-12 00 Studies of the Clinical Effects of Bacteriophage
J F Kessel, Los Angeles, Calif

B-III

UNIVERSITY OF CALIFORNIA MEDICAL SCHOOL
Medical School Building
(Parnassus and Second Avenues)
Medical Teaching Room, First Floor
(Capacity—34)

- 9 00-10 00 Demonstration Clinic Diseases of the Nervous System
Samuel D Ingham, Los Angeles, Calif
- 10 00-11 00 Myotonia Congenita, Myasthenia Gravis and Familial Periodic Paralysis.
Milton B Lennon
- 11 00-12 00 Hourglass Tumors of the Spinal Cord
Howard A Brown

B-IV

UNIVERSITY OF CALIFORNIA MEDICAL SCHOOL
Medical School Building
(Parnassus and Second Avenues)
Surgical Teaching Room, First Floor
(Capacity—20)
Medico-Surgical Clinic

- 9 00-10 00 The Irritable Colon as a Factor in Intestinal Stasis
Elmer L. Eggleston, Battle Creek, Mich
- 10 00-11 00 Diseases of the Colon Ulcerative Colitis
Montague S Woolf
- 11 00-12 00 Chronic Colitis
Fred H Kruse

B-V

UNIVERSITY OF CALIFORNIA MEDICAL SCHOOL
Medical School Building
(Parnassus and Second Avenues)
Pathological Laboratory, Third Floor
(Capacity—15)

- 9 00- 9 30 A Further Study of a White Family Showing Elliptical Erythrocytes
Warren C Hunter, Portland, Ore
- 9 30- 9 45 Agranulocytic Syndromes
Edwin E Osgood, Portland, Ore
- 9 45-10 00 The Reticulocyte Stain
Edwin E Osgood, Portland, Ore
- 10 00-12 00 Interesting and Unusual Blood Smears Laboratory Demonstration
Stacy R Mettier and James F Rinehart

Thursday, April 7, 1932 (Continued)

C-I

UNIVERSITY OF CALIFORNIA MEDICAL SCHOOL

College of Dentistry Building
(Parnassus and First Avenues)

Amphitheater, Third Floor

(Capacity—168)

Mycotic Infections Coccidioides, Sporotrichosis,
Actinomycosis

- 9 00-10 30 Etiology and Epidemiology
Karl F Meyer and Staff
10 30-12 00 Clinical Aspects
Howard Morrow and Staff

C-II

UNIVERSITY OF CALIFORNIA MEDICAL SCHOOL

College of Dentistry Building
(Parnassus and First Avenues)

Classroom A, Third Floor

(Capacity—82)

- 9 00-10 00 The Three Common Types of Blood Pressure in Vascular Disease
Willard J Stone, Pasadena, Calif
10 00-12 00 Evolution of Urinary Excretion with Reference to Renal Function
I Excretion of Invertebrates
Frank Hinman

C-III

UNIVERSITY OF CALIFORNIA MEDICAL SCHOOL

College of Dentistry Building
(Parnassus and First Avenues)

Classroom B, Third Floor

(Capacity—40)

- 9 00- 9 45 Nontuberculous Spinal Arthritis
W Paul Holbrook, Tucson, Ariz
Clinic on Tuberculosis
9 45-10 30 Orthopedic
Geo C Hensel
10 30-11 15 Urological
Sidney Olsen
11 15-12 00 Pulmonary Tuberculosis
Sidney J Shipman

D-I

UNIVERSITY OF CALIFORNIA

Life Sciences Building, Berkeley

Room 2000, Second Floor

(No Program on Thursday)

Thursday, April 7, 1932 (Continued)

D-II

UNIVERSITY OF CALIFORNIA

Life Sciences Building, Berkeley

Room 2003, Second Floor

(Capacity—208)

- 10 00-10 30 Photosensitization.
Harold F Blum
- 10 30-11 00 Morphine Addiction
Lawrence E Detrick
- 11 00-11 30 Clinical Aspects of Splenic Physiology
Eric Ogden

D-III

UNIVERSITY OF CALIFORNIA

Life Sciences Building, Berkeley

Room 2503, Second Floor

(Capacity—208)

- 10 00-10 30 The Normal Variation in the Clinically Important Blood Constituents of Women and Their Possible Significance
Ruth Okey
- 10 30-11 00 The Role of Vitamin B in the Treatment of Undernutrition in Children
A F Morgan
- 11 00-11 30 The Treatment of Carcinoma in Experimental Animals by Low Pressure
Edward S Sundstroem

Note The following laboratory demonstrations will be held on Thursday morning in the Life Sciences Building

Demonstration in the Field of Human Amebiasis (Room 5077)
C A Kofoid

Mode of Action of Bacteriophage (Room 3543)
A. P Krueger

Demonstration of Low Pressure Treatment of Carcinoma in Experimental Animals (Room 5517)
Edward S Sundstroem

No tickets will be required for these demonstrations

The laboratories of Biochemistry, Physiology, Bacteriology, Household Science and Zoology will be open for inspection

Institute of Experimental Biology

Demonstrations will be held by Professor Herbert M Evans and Staff in the Anatomy Department, Life Sciences Building

E-I

STANFORD UNIVERSITY MEDICAL SCHOOL

Medical School Building
(Clay and Webster Streets)

Lane Hall, Second Floor

(Capacity—333)

- 10 00-11 00 Medical Clinic
Arthur L Bloomfield
- 11 00-12 00 Medical Clinic
William F Cheney

Thursday, April 7, 1932 (Continued)

E-II

STANFORD UNIVERSITY HOSPITAL,
(Clay and Webster Streets)
Physiotherapy Department, Second Floor
(Capacity—15)

9 00-12 00 Clinic on Physical Therapeutics
H L Langnecker

E-III

STANFORD UNIVERSITY HOSPITAL,
(Clay and Webster Streets)
Operating Amphitheater, Sixth Floor
(Capacity—71)

9 00- 9 45 Clinic on Postoperative Pulmonary Complications
Maurice C Pinecoffs, Baltimore, Md
9 45-10 30 Anesthesia from the Internists Standpoint
Caroline B Palmer and Staff
10 30-11 15 Whole Blood Transfusion, Demonstration of Technique
LeRoy Brooks
11 15-12 00 Bone Tumors A General Practice Problem
Merrill Mensor

E-IV

STANFORD UNIVERSITY HOSPITAL,
Children's Ward, Fourth Floor
(No Program on Thursday)

E-V

STANFORD UNIVERSITY MEDICAL SCHOOL,
Medical School Building
(Clay and Webster Streets)
Room 311, Third Floor
(Capacity—112)

9 00- 9 30 Treatment of Pernicious Anemia
Cyrus C Sturgis, Ann Arbor, Mich
9 30-10 00 A Study of Glycosuria in Hyperthyroidism
Blair Holcomb, Portland, Ore
10 00-10 30 Ovary-Stimulating Substances in the Blood of Women
C Frederic Fluhmann
10 30-11 00 Addison's Disease with Tumors of Suprarenals
Donald A Carson
11 00-11 30 Results After Total Thyroidectomy
Willard E Kay and Philip K Gilman
11 30-12 00 Experimental Hypophysectomy
Frederick L Reichert

Thursday, April 7, 1932 (Continued)

F-I

STANFORD UNIVERSITY MEDICAL SCHOOL

Nurses' Home

(2340 Clay Street)

Assembly Room, First Floor

(Capacity—280)

- 9 00- 9 45 The Diagnosis and Treatment of Bronchiectasis
James Alex Miller, New York, N Y
- 9 45-10 30 A Study of the Bronchial, Pulmonary and Lymphatic Circulation of the Lungs
Under Various Pathological Conditions, Experimentally Produced
Emile F Holman
- 10 30-11 15 A Discussion of the Relationship of Upper Respiratory Infection to Acute and
Chronic, Tuberculous and Pyogenic Pulmonary Disease
Philip H Pierson
- 11 15-12 00 Infection of the Accessory Nasal Sinuses as a Factor in Diseases of the Lungs
Samuel H Hurwitz and Edward Sewall
-

F-II

STANFORD UNIVERSITY MEDICAL SCHOOL

Nurses' Home

(2340 Clay Street)

Room 5, First Floor

(Capacity—74)

- 9 00- 9 30 Rocky Mountain Spotted Fever
G Gill Richards, Salt Lake City, Utah
- 9 30-10 00 Demonstration of Coccidioidal Granuloma
Ernest Dickson and Staff
- 10 00-10 30 Remarks on Bone Marrow Biopsy Studies
Harry A Wyckoff and Loren R Chandler
- 10 30-11 00 Studies in the Behavior of a Benign Transplantable Tumor
Ludwig A Emge
- 11 00-11 20 Diuretics and the Mechanisms of Diuresis
Andrew B Stockton
- 11 20-11 40 Experimental Studies of Epinephrine Substitutes
Maurice L Tanter
- 11 40-12 00 Protective Action of Colloidal Dyes on Intoxication
Paul J Hanzlik
-

F-III

STANFORD UNIVERSITY MEDICAL SCHOOL

Nurses' Home

(2340 Clay Street)

Room 4, First Floor

(Capacity—80)

- 9 00- 9 30 Oxygen in Coronary Heart Disease
Robt I Rizer, Minneapolis, Minn
- 9 30-10 00 Arterial Hypertension
C J Jennings, Detroit, Mich
- 10 00-10 30 Anomalies of the Great Vessels of the Chest
William Dock
- 10 30-11 00 Graphic Records of Gallop Rhythm
J K Lewis

Thursday, April 7, 1932 (Continued)

- 11 00-11 20 Prediction and Measurement of the Cardiac Silhouette
Robert R Newell
- 11 20-11 40 Circulatory Changes in the Fundus Oculi
Hans Barkan
- 11 40-12 00 Pitfalls in the Diagnosis of Hydrothorax in Cardiac Decompensation
Wm W Newman

G

STANFORD UNIVERSITY MEDICAL SCHOOL,
Preclinical Departments, Palo Alto
(No Program on Thursday)

II-I

SAN FRANCISCO HOSPITAL,
(22nd Street and Potrero Avenue)
University of California Service
Ward I, First Floor
(Capacity—20)

- 9 00-10 00 Ward Rounds
LeRoy H Briggs
- 10 00-11 00 Ward Rounds
Sydney R Miller, Baltimore Md

II-II

SAN FRANCISCO HOSPITAL,
(22nd Street and Potrero Avenue)
University of California Service
Amphitheater, Third Floor
(Capacity—100)

- 9 00- 9 30 Pulmonary Emphysema
Frank R Mount, Oregon City Ore
- 9 30-10 00 The Paranasal Sinus Problem in Internal Medicine
A D Dunn, Omaha, Nebr
- 10 00-10 30 Atelectasis, Clinical and Experimental
H W Stephens and M Printzmetel
- 10 30-11 00 Lesions of the Esophagus
F D Heegler
- 11 00-12 00 Medico-Pathological Conference
Glauville Y Rusk and Medical and Surgical Staffs

II-III

SAN FRANCISCO HOSPITAL
(22nd Street and Potrero Avenue)
University of California Service
Council Room, First Floor
(Capacity—35)

The Exhibition of Gall Stones and Exhibition of Anatomical Drawings will be
still on display

Thursday, April 7, 1932 (Continued)

H-IV

SAN FRANCISCO HOSPITAL
(22nd Street and Potrero Avenue)
University of California Service
Ward 30, Fifth Floor
(Capacity—20)

- 9 00-10 00 Ward Rounds Tuberculosis in Children
J Arthur Myers, Minneapolis, Minn
10 00-11 30 Ward Rounds Tuberculosis in Infants, with Special Reference to Prognosis
Wm Anthony Reilly
11 30-12 00 Intravenous Urographv in Children
Amos U Christie

I

CHIDREN'S HOSPITAL
(3700 California Street)
Recreation Hall, Annex, First Floor
(Capacity—100)
Communicable Disease Department

- 9 00- 9 45 Use of Spencer-Parker Vaccine in Rocky Mountain Spotted Fever
R R Parker, Hamilton, Mont
9 45-10 30 Meningococcus Infections
E B Shaw and H E Thelander
10 30-11 15 Blood Picture in Treated, Untreated and in Complicated Pertussis
Hildegard Henderson and H E Thelander
11 15-12 00 Blood Grouping in Infectious Diseases
E B Shaw and Kathleen Kilgariff

J

FRANKLIN HOSPITAL.
(14th and Noe Streets)
Nurses' Lecture Room, Second Floor
(Capacity—30)

- 9 00-10 00 Clinic on Rheumatic Heart Disease and Subacute Bacterial Endocarditis
Geo Morris Piersol, Philadelphia, Pa
10 00-10 30 Clinic on Degenerative Circulatory Diseases
Emmett C Taylor
10 30-11 00 Dietary Principles as Related to Particular Intestinal Conditions
Elbridge J Best
11 00-11 30 Clinic on Interesting Dermatoses
Harry E Alderson and Stuart C Way
11 30-12 00 Diagnosis and Treatment of Chronic Epidemic Encephalitis
Walter F Schaller

K

FRENCH HOSPITAL,
(Geary Street and 5th Avenue)
Auditorium, First Floor
(Capacity—250)

- 9 00- 9 15 The Treatment of Syphilitic Aortitis
T Homer Coffen, Portland, Ore

Thursday, April 7, 1932 (Continued)

- 9 15-10 30 Heart Block
Eugene S Kilgore
- 10 30-11 15 A Presentation of Cases and Moving Pictures of Auricular Fibrillation and a
Discussion of Treatment
Hariv Spiro and Win W Newman
- 11 15-11 45 Diseases of the Thyroid Gland Medical and Surgical Aspects
Carl L Hoag
- 11 45-12 00 Discussion of Diseases of the Thyroid Gland
W W Washburn

L

LAGUNA HONDA HOME
(7th Avenue and Dewey Blvd) ,
Stanford University Service
Chapel First Floor, Infirmary Building
(Capacity—300)

- 9 00-10 00 Differential Diagnosis of Bronchogenic Carcinoma
Marr Bisailon, Portland, Ore
- 10 00-11 00 Demonstration of X-Ray Films
Edward Leef
- 11 15-12 00 Problems in Hematology
Garnett Cheney

M

LETTERMAN GENERAL HOSPITAL
(United States Presidio)
(No Program on Thursday)

N

MARINE HOSPITAL
(14th Avenue and Lake Street)
Board Room No 109, First Floor
(Capacity—20)

- 9 00- 9 30 Clinical Studies on the Treatment of Amebiasis with Carbarsone
Win M James, Panama R P Hamilton H Anderson and Dorothy Koch
- 9 30-10 00 Gastric and Duodenal Ulcers
Robert A Jones
- 10 00-10 30 Malaria
Walter P Griffey
- 10 30-11 00 Amebiasis
Richard L Wrough
- 11 00-11 30 Paresis
Elmer A Carberry
- 11 30-12 00 Arteriosclerosis
James F Worley

Thursday, April 7, 1932 (Continued)

O

MARY'S HELP HOSPITAL,
(145 Guerrero Street)
Lecture Room, First Floor
(Capacity—35)

- 9 00-10 00 Neutrophilic Leukopenia Report of a Case
Andrew Bonthuis, Pasadena, Calif
- 10 00-10 30 Allergy in Children
Crawford Bost
- 10 30-11 00 Medical Aspects of the Toxemias of Pregnancy
Hans von Geldern
- 11 00-11 30 Malignant Neutropenia
Frank E. Stiles
- 11 30-12 00 Intractable Diarrhea
Alfred C. Reed

P-I

MOUNT ZION HOSPITAL
Nursing School Auditorium, First Floor
(2345 Sutter Street)
(Capacity—300)

- 9 00-10 00 A Treatment of Rheumatic Cardiovascular Disease with Special Reference to
Intravenous Vaccine
Wm D. Stroud, Philadelphia, Pa
- 10 00-10 30 Neuromata of the Appendix
Franklin I. Harris and Morris J. Groper
- 10 30-11 00 Perinephric Abscess
Harold Brunn
- 11 00-11 30 Autotransfusion from the Pleura
A. Lincoln Brown
- 11 30-12 00 Accidental Electrical Shock
Felix Pearl

P-II

MOUNT ZION HOSPITAL
(2345 Sutter Street)
Nursing School Classroom, First Floor
(Capacity—47)

- 9 00- 9 30 The Significance of Fever
Hobart A. Remann, Minneapolis, Minn
- 9 30-10 00 Demonstration of the Use of Radiotherapy in Diseases of the Circulation
C. F. Tenney, New York, N. Y.
- 10 00-10 30 Pyrodiathermy
Lloyd Bryan
- 10 30-11 00 Medical Aspects of Diseases of the Prostate
L. C. Jacobs
- 11 00-11 30 Relief of Paralytic Ileus by Spinal Anesthesia
E. H. Bolze
- 11 30-12 00 Immune Rabbit Serum in Staphylococcal Septicemia
Morris J. Groper

Thursday, April 7 1932 (Continued)

ST FRANCIS HOSPITAL
(1190 Bush St)
(No Program on Thursday)

R

ST JOSEPH'S HOSPITAL
(Park Hill and Buena Vista Avenues)
(No Program on Thursday)

S

ST LUKE'S HOSPITAL
(27th and Valencia Streets)
(No Program on Thursday)

I'

ST MARY'S HOSPITAL
(Hayes and Stanyan Streets)
(No Program on Thursday)

U

SHRINERS HOSPITAL FOR CRIPPLED CHILDREN
(19th Avenue and Moraga Street)
(No Program on Thursday)

I'

SOUTHERN PACIFIC HOSPITAL
(Fell and Baker Streets)
Auditorium Fifth Floor
(Capacity—125)

- 9 00- 9 30 Demonstration Clinic Gastro-intestinal Diseases
John Dudley Dunham, Columbus, Ohio
- 9 30-10 00 Bidirectional Ventricular Tachycardia Apparently Due to Digitalis
Wm H Leake, Los Angeles, Calif
- 10 00-10 30 Management of Peptic Ulcer Among Railroad Employees
Philip K Brown
- 10 30-11 00 The Place of Laboratory Examinations in the Treatment of Diabetes
Emmett Allen
- 11 00-12 00 Ward Rounds
Philip K Brown and Staff
-

II

HISTORICAL PROGRAM
(No Program on Thursday)

Program of the San Francisco Meeting

A-I

Friday, April 8, 1932
 UNIVERSITY OF CALIFORNIA HOSPITAL,
 (Parnassus and Third Avenues)
 Toland Hall, First Floor
 (Capacity—167)

- 9 00-11 00 Rocky Mountain Spotted Fever
 R R Parker, Hamilton, Mont, G Gill Richards, Salt Lake City, Utah,
 and Ernest L. Walker
- 11 00-12 00 Relapsing Fever
 Karl F Meyer
-

A-II

UNIVERSITY OF CALIFORNIA HOSPITAL,
 (Parnassus and Third Avenues)
 Room 310, Third Floor
 (Capacity—35)

- 9 00-10 00 Chemistry of Intestinal Obstruction
 Francis S Smith
- 10 00-11 00 Certain Experimental Studies in Intestinal Obstruction
 M Laurence Montgomery
- 11 00-12 00 Treatment of Intestinal Obstruction
 Robertson Ward
-

A-III

UNIVERSITY OF CALIFORNIA HOSPITAL,
 (Parnassus and Third Avenues)
 Ward A, Fourth Floor
 (Capacity—15)

- 9 00-10 00 Ward Rounds Diseases of Blood Formation
 J H Musser, New Orleans, La
- 10 00-12 00 Ward Rounds
 Ernest H Falconer and Stacy R Mettier
-

A-IV

UNIVERSITY OF CALIFORNIA HOSPITAL,
 (Parnassus and Third Avenues)
 Ward E, Fifth Floor
 (Capacity—15)

- 9 00-10 00 Ward Rounds
 Leander A Riely, Oklahoma City, Okla
- 10 00-11 00 Ward Rounds An Instance of Lymphomatosis Radiologically Cured
 Henry Harris
- 11 00-12 00 Ward Rounds
 Irwin C Schumacher
-

B-I

UNIVERSITY OF CALIFORNIA MEDICAL SCHOOL,
 Medical School Building
 (Parnassus and Second Avenues)
 Cole Hall, Third Floor
 (Capacity—200)

- 9 00-10 00 Peptic Ulcer
 Clement R Jones, Pittsburgh, Pa

Friday, April 8, 1932 (Continued)

- 10 00-11 00 Unusual Gastric Lesions
J Homer Woolsey and Fred H Kruse
11 00-12 00 X-Ray Therapy of Gastric Lesions
Howard E Ruggles
-

B-II

UNIVERSITY OF CALIFORNIA MEDICAL SCHOOL
Medical School Building
(Parnassus and Second Avenues)
Pharmacology Laboratory, Third Floor
(Capacity—50)

- 9 00-12 00 Clinico-Pathological Conference Cardiovascular Diseases
Wm S Middleton, Madison, Wis, Henry L Ulrich, Minneapolis, Minn,
Wm J Kerr, Gordon E Hein and Charles L Connor
-

E-III

UNIVERSITY OF CALIFORNIA MEDICAL SCHOOL
Medical School Building
(Parnassus and Second Avenues)
Medical Teaching Room, First Floor
(Capacity—34)

- 9 00-10 00 Studies in Psychopathic Personalities
Hermann M Adler,
10 00-11 00 Demonstration of Nerve Cases
Richard W Harvey
11 00-12 00 Neurological Aspects of Pernicious Anemia
Mervyn H Hirschfeld
-

B-IV

UNIVERSITY OF CALIFORNIA MEDICAL SCHOOL
Medical School Building
(Parnassus and Second Avenues)
Surgical Teaching Room, First Floor
(Capacity—20)

- 9 00- 9 45 Diverticulosis of the Colon in Relation to Chronic Arthritis
Ernest C Fishbaugh, Los Angeles, Calif
9 45-10 30 Polyposis of the Large Bowel
Montague S Woolf
10 30-12 00 Bone Tumors Diagnosis and Treatment
Edwin I Bartlett and Robert S Stone
-

C-I

UNIVERSITY OF CALIFORNIA MEDICAL SCHOOL
College of Dentistry Building
(Parnassus and First Avenues)
Amphitheater, Third Floor
(Capacity—168)

- 9 00-10 00 Demonstration of Cases
David P Barr, St Louis, Mo

Friday, April 8, 1932 (Continued)

- 10 00-11 00 Myxedema
H Lissner
- 11 00-12 00 Diabetes
H Clare Shepardson

C-II

UNIVERSITY OF CALIFORNIA MEDICAL SCHOOL
College of Dentistry Building
(Parnassus and First Avenues)
Classroom A, Third Floor
(Capacity—82)

- 9 00- 9 30 Experimental Studies of the Effects of Potassium Bichromate on the Monkey's
Kidney
Warren C Hunter, Portland, Ore
- 9 30-10 00 Glomerular Changes in the Kidneys of Rabbits and Monkeys Produced by
Uranium Nitrate, Mercuric Chloride and Potassium Bichromate
Warren C Hunter, Portland, Ore
- 10 00-12 00 Evolution of Urinary Excretion with Reference to Renal Function
II Excretion of Vertebrates
Frank Hinman

C-III

UNIVERSITY OF CALIFORNIA MEDICAL SCHOOL
College of Dentistry Building
(Parnassus and First Avenues)
Classroom B, Third Floor
(Capacity—40)

- 9 00- 9 45 Treatment of Pernicious Anemia
Cyrus C Sturgis, Ann Arbor, Mich
- 9 45-10 30 Chemotherapy of Amebiasis
Hamilton H Anderson
- 10 30-11 15 New Drugs in Cardiac Disease
Dudley W Bennett
- 11 15-12 00 New Drugs Used in Diagnosis
Chauncey D Leake

D

UNIVERSITY OF CALIFORNIA
Preclinical Departments, Medical School
Life Sciences Building, Berkeley
(No Program on Friday)

E-I

STANFORD UNIVERSITY MEDICAL SCHOOL
Medical School Building
(Clay and Webster Streets)
Lane Hall, Second Floor
(No Program on Friday)

Friday, April 8, 1932 (Continued)

E-II

STANFORD UNIVERSITY HOSPITAL
(Clay and Webster Streets)
Physiotherapy Department, Second Floor
(No Program on Friday)

E-III

STANFORD UNIVERSITY HOSPITAL
Operating Amphitheater, Sixth Floor
(No Program on Friday)

E-IV

STANFORD UNIVERSITY HOSPITAL
(Clay and Webster Streets)
Children's Ward, Fourth Floor
(Capacity—15)

9 00-12 00 Pediatric Ward Rounds Demonstration of Cases and Discussion of Special
Topics
Harold K. Faber and Staff

E-V

STANFORD UNIVERSITY MEDICAL SCHOOL
Medical School Building
Room 311, Third Floor
(No Program on Friday)

F-I

STANFORD UNIVERSITY MEDICAL SCHOOL
Nurses' Home
(2340 Clay Street)
Assembly Room, First Floor
(Capacity—280)

9 00- 9 45 Clinic on Bright's Disease
Thomas Addis
9 45-10 30 Nephritis and Nephrosis
E. T. Bell, Minneapolis, Minn.
10 30-11 00 Physiological Reaction of Insulin
Dwight E. Shepardson
11 00-11 30 High Fat Modification of Joslin's Diabetic Card
Horace Gray and Jean Stewart
11 30-12 00 Disorders of Growth, Illustrated with Lantern Slides
Horace Gray and L. M. Bayer

F-II

STANFORD UNIVERSITY MEDICAL SCHOOL
Nurses' Home
(2340 Clay Street)
Room 5, First Floor
(Capacity—74)

9 00- 9 30 Prognosis for Cholecystitis Based on a Clinical Study
John M. Blackford, Seattle, Wash.

Friday, April 8, 1932 (Continued)

- 9 30-10 00 Cholecystography
Edward Leef.
- 10 00-10 30 Clinical and Pathological Demonstrations
Günther W. Nagel
- 10 30-11 00 Diagnosis of Amebiasis
Herbert Gunn
- 11 00-11 30 Jaundice
Donald A. Carson
- 11 30-12 00 Indigestion and Related Problems
Arthur I. Bloomfield and Associates

F-III

STANFORD UNIVERSITY MEDICAL SCHOOL

Nurses' Home
(2340 Clay Street)
Room 4, First Floor
(Capacity—80)

- 9 00- 9 30 Cerebral Vascular Syndromes
C. J. Rohwer, Seattle, Wash.
- 9 30-10 00 Demonstration of Patients
Walter F. Schaller and Thomas S. Inman
- 10 00-10 30 The 1931 Polyneuritis Demonstration of Patients
Julian M. Wolfsohn
- 10 30-11 00 Clinical Studies in Epilepsy
Helen Hopkins-Detrick
- 11 00-11 20 Study of Variations in the Roentgenological Appearance of Cerebral Arteries
Melvin Somers
- 11 20-11 40 Anionic Bismuth Therapy in Neurosyphilis
Henry G. Mehrtens and Pearl S. Pomppert
- 11 40-12 00 Typical and Atypical Cranial Neuralgias
Frederick L. Reichert

G

STANFORD UNIVERSITY MEDICAL SCHOOL

Preclinical Departments, Palo Alto
Anatomy Lecture Room
(Capacity—80)
Department of Anatomy

- 10 00-10 15 Modification of the Uterine Vascular Rhythms by Certain Pharmacological Agents
J. E. Markee
- 10 15-10 30 Neurologic Mechanism in Spinal Standing in the Cat
J. C. Hinsey
- 10 30-10 45 Hereditary Alopecia Anemia and Duplication of Parts in Some Laboratory Animals
C. H. Danforth
- 10 45-11 30 Bacteriophage as a Therapeutic Agent A Summary of Clinical Reports Made to the Department of Bacteriology
E. W. Schultz

Friday, April 8, 1932 (Continued)

H

SAN FRANCISCO HOSPITAL
(22nd Street and Potrero Avenue)
Stanford University Service
(Medical Amphitheater, Third Floor, Operating Pavilion)
(Capacity—105)

- 9 00-10 00 Moving Picture Film Demonstrating the Effects of Various Irregularities
on Dogs' Hearts
Carl J Wiggers, Cleveland, Ohio
- 10 00-10 30 Cardiac Asthma
Charles E Watts, Seattle, Wash
- 10 30-11 00 Bronchial Asthma
Edward Matzger
- 11 00-11 30 Clinical Studies of Circulatory Adaptations
J Marion Read
- 11 30-12 00 Ward Rounds
Harold P Hill

I

CHILDREN'S HOSPITAL
(3700 California Street)
(No Program on Friday)

J

FRANKLIN HOSPITAL
(14th and Noe Streets)
(No Program on Friday)

K

FRENCH HOSPITAL
(Geary Street and 5th Avenue)
Auditorium, First Floor
(Capacity—250)

- 9 00- 9 30 Treatment of Typhoid Fever with Bacteriophage
Thomas C McCleave, Berkeley, Calif
- 9 30-10 00 Report of a Case of Colon Bacillus Meningitis Associated with an Unusual
Spinal Anomaly
Bradford F Dearing
- 10 00-10 30 Laboratory Demonstrations
- 1 Easy Measurements of Red Blood Cell Diameter in Pernicious Anemia
by Eve's Halometer
 - 2 Urine Pregnancy Test by Friedman Modification of the Aschheim-
Zondek Test
- Marion H Lippman
- 10 30-11 15 Migrating Pneumonia A Study of Certain Factors which Determine Sites
of Migration, Newer Principles of Treatment
William B Faulkner, Jr, and Aime N Fregeau
- 11 15-12 00 Middle Lobe Pulmonary Abscesses Problems in Diagnosis and Treatment
William B Faulkner, Jr, and Philip G Corliss

Friday, April 8, 1932 (Continued)

L

LAGUNA HONDA HOME
(7th Avenue and Dewey Blvd)
(No Program on Friday)

M-I

LETTERMAN GENERAL HOSPITAL
(United States Presidio)
Assembly Room
(Capacity—100)

- 9 00-10 00 Hematoporphyrimuria
Verne Mason, Los Angeles, Calif.
10 00-11 00 Diabetes Mellitus
Major D B Faust, M C
11 00-12 00 Types of Jaundice Differential Diagnosis and Treatment
Major D B Faust, M C
-

M-II

LETTERMAN GENERAL HOSPITAL
(United States Presidio)
Ward S-1
(Capacity—60)

- 9 00-10 30 Dementia Praecox, with Presentation of Cases
Lt Col T D Woodson, M C
10 30-12 00 Selected Psychiatric Cases
Major T L Long, M C
-

M-III

LETTERMAN GENERAL HOSPITAL
(United States Presidio)
Medical Wards
(Capacity—15)

- 9 00-10 00 Ward Rounds
James G Carr, Chicago, Ill
10 00-11 00 Ward Rounds Cardiac Section
Major W C Munly, M. C
11 00-12 00 Ward Rounds Selected Medical Cases
Col L L Smith M C
-

N

MARINE HOSPITAL
(14th Avenue and Lake Street)
(No Program on Friday)

O

MARY'S HELP HOSPITAL
(145 Guerrero Street)
Lecture Room, First Floor
(Capacity—35)

- 9 00- 9 30 Nontuberculous Spinal Arthritis
W Paul Holbrook, Tucson, Ariz

Friday, April 8, 1932 (Continued)

- 9 30-10 00 Studies of the Relationship of Dental Infections to So-Called Focal Infections
Frank R Menne and Miriam Luetin, Portland, Ore
- 10 00-10 30 Pathological Types of Arthritis
Zera E Bolin
- 10 30-11 00 Arthritis of the Menopause
J Morrille George
- 11 00-11 30 Studies in the Etiology of Arthritis
Leon Parker
- 11 30-12 00 Treatment of Arthritis
Merrill C Mensor

P-I

MOUNT ZION HOSPITAL

(2345 Sutter Street)

Nursing School Auditorium, First Floor

(Capacity—300)

- 9 00- 9 30 Diseases of the Gastro-intestinal Tract
Walter C Alvarez, Rochester, Minn
- 9 30-10 00 Luminal Dermatitis
Normal N Epstein
- 10 00-10 30 Diabetes Insipidus
Russell F Rypins
- 10 30-11 00 Mechanical Influence on Clinical Heart Function of Pericardial Lesions
John J Sampson
- 11 00-11 30 The Severe Chronic Intractable Type of Bronchial Asthma, Reason for Failure
Fred Firestone
- 11 30-12 00 Exudative Lesions in Pulmonary Tuberculosis
William C Voorsanger

P-II

MOUNT ZION HOSPITAL

Nursing School Auditorium, First Floor

(No Program on Friday)

Q

ST FRANCIS HOSPITAL

(1190 Bush Street)

Nurses' Lecture Room, Basement

(Capacity—60)

- 9 00- 9 30 The Heart in Hypothyroidism
Homer Rush, Portland, Ore
- 9 30-10 00 Angina Pectoris
Bernard Kaufman
- 10 00-10 30 A Demonstration and Discussion of the Pathology of Coronary Disease
A M Moody
- 10 30-11 00 Unusual Blood Reactions to Infection
Philip K Brown

Friday, April 8, 1932 (Continued)

11 00-11 30 Atypical Blood Conditions in Children

William P Lucas

11 30-12 00 A Physiological Comparison of High and Low Carbohydrate Feeding in
Diabetes

Dwight Ervin

R

St JOSEPH'S HOSPITAL
(Park Hill and Buena Vista Avenues)
(No Program on Friday)

S

ST LUKE'S HOSPITAL
(27th and Valencia Streets)
(No Program on Friday)

T

ST MARY'S HOSPITAL
(Hayes and Stanyan Streets)
(No Program on Friday)

U

SHRINERS HOSPITAL FOR CRIPPLED CHILDREN
(19th Avenue and Moraga Street)
(No Program on Friday)

V

SOUTHERN PACIFIC HOSPITAL
(Fell and Baker Streets)
(No Program on Friday)

W

LANE LIBRARY
(Clay and Webster Streets)
(Capacity—100)

9 00-12 00 Anatomical Traditions of the Renaissance and Their Relation to the Modern Teaching of Anatomy

Charles J Singer, London, Eng, Sanford V Larkey, John de C M Saunders, and others

Cutaneous Manifestations of Systemic Disease*†

By UDO J WILE, M D , *Ann Arbor, Michigan*

MORE than a half a century has elapsed since cutaneous medicine became established as a recognized special field. The development of specialties in general has come about rather slowly, receiving initiative from the great epochs of modern medical science, notably the rational pathology of the Virchow school and the application to the theory and practice of medicine of the principles of modern bacteriology and immunity.

Dermatology may be said in some respects to have had an unfortunate and precipitous birth. It did not develop gradually but was rather abruptly established as a result of the classification of dermatoses based upon pure morphologic characteristics by the early founders of the Vienna school. This has resulted in the development of a cumbersome, awkward, and somewhat irrational nomenclature.

The early interpretation of pure morphologic pictures as these occur in the skin led away from, rather than

toward, the concept of general morbid processes. The natural result of this schism from the domain of general medicine was the development of a field with its own peculiar pathology, and with an ever-widening breach between its confines and the pathologic processes which affect other systems.

A science based upon such superficial characteristics could not long endure as such. The last two decades, therefore, have seen a great change in the interpretation of disease processes in the skin. The recognition of the integument as an organ of fundamental importance in the general physiology of the body, its function as a vast heat-regulating mechanism, as an excretory and secretory organ, and more latterly its recognition in the important biophysical and biochemical activities of the organism, are rapidly aligning disease conditions in the skin with the general pathologic state of the individual. Each year sees more and more so-called essential dermatoses proved and accepted as the cutaneous reflections of systemic morbid processes.

Cutaneous medicine therefore concerns itself with the concept of the skin and its appendages, as a complex organ which graphically reflects systemic disease processes in a vast variety of what might be termed *reac-*

*Studies and Contributions of the Department of Dermatology and Syphilology, University of Michigan Medical School, service of Dr Udo J Wile.

†Read at a Stated Meeting of the New York Academy of Medicine, December 3, 1931. Received for publication, December 30, 1931.

tions Conversely, it also serves as an excellent yardstick whereby may be evaluated and measured standards of good health

The so-called essential skin diseases have in the course of the last few years been narrowed down to local infections, both bacterial and mycotic, and to a few benign and malignant growths. The several unexplained inflammatory diseases in the skin such as lichen planus and psoriasis, may in our ignorance still be regarded as peculiar to the integument. The ultimate elucidation of their nature, however, may well show them to be the manifestations of a general rather than a local pathologic condition

It is manifestly impossible to enumerate or to discuss in detail all of the various skin manifestations of systemic disease. It would, I think, be far better to emphasize the theme suggested by taking two texts: first, the subject of focal infection in its relation to cutaneous disorders; and, second, the intimate relation of the skin to the group of so-called lymphoblastomatous diseases

Among the many theories elaborated to explain the phenomena of morbid processes, none has seemed at first glance so attractive, so readily applicable to many diseases, as that of bacterial foci from which systemic infections take place. Following, as it did, in logical sequence, the identification of specific microbes as causative agents in the production of disease, and the subsequent knowledge of bacterial sepsis, it is easily comprehensible why the theory of focal infection should have been readily applied to hitherto unknown etiologic entities

That focal infection has passed from a scientific theory to a proved principle cannot be gainsaid. The work of Billings, Rosenow, Holman and many others in this country and abroad has established beyond a peradventure that its application to certain disease processes fulfils all scientific postulates. However, it must also be admitted that, like uric acid, the theory of focal infection has had woven about its application as much of fiction as of truth.

There is a basic misconception and rather widely current confusion in the minds of many who have written and spoken on this subject, between the terms, focus of infection and focal infection. The two are frequently loosely and synonymously applied in both writing and discussion, when in fact they should be sharply differentiated.

Billings described a focus of infection as a circumscribed area of tissue infected with pathogenic organisms. Holman has pointed out, therefore, that any condition resulting from the systemic dissemination of bacteria from the source or focus becomes a focal infection. It is therefore self-evident that focal infection results from foci of infection and the two terms, although related sequentially, have different identities and must not be confused.

Perhaps the simplest example of proven focus and consequent focal dissemination is the chancre of syphilis, here we have a nidus of pathogenic organisms leading to more or less rapid dissemination and to remote morbid processes in the skin, viscera, and mucous membranes, thus representing admirably a focal infective process.

It seems quite natural that, in the

ten or more years since Billings' first paper on focal infection, the theory should have found favor among dermatologists, and an earnest effort should have been made to apply it to our many obscure etiological problems. When the initial wave of enthusiasm passed, it was found as in other advances in medical science, that something new had been added to our knowledge of the causation of disease, but much was left over to be explained by other theories. It is safe to state that at some time or other almost every etiologically obscure dermatosis has been said to result from a focus of infection, but only a few have stood the rigid scrutiny of scientific accuracy and have been established as of such origin.

With the clear-cut definition of a focus of infection as a nidus of pathogenic organisms, and of focal infection as the expression of systemic invasion by these organisms, very rigid criteria should be applied to a disease, together with convincing experimental evidence, before it may be accepted as an example of a focal infective process. In by far the majority of examples in cutaneous medicine, where focal infection has been suggested as the cause of symptoms, the case has been made on suggestive criteria and on clinical data. Thus, one observer with a series of cases of, let us say, alopecia areata, in which dental caries has co-existed, expressed the opinion that the latter as foci caused the former. His view was perhaps strengthened by the clinical observation that the alopecia disappeared after removal of the alleged foci. I shall hope to show later that while such evidence is perhaps suggestive or presumptive, it lacks scientific

accuracy and does not sufficiently support accepted postulates for cause and effect in disease.

At some time or other the following conditions have been considered to be due to foci, and therefore examples of focal infective processes: urticaria, urticaria pigmentosa, eczema, the erythema multiforme group, cutaneous tuberculosis and the tuberculides, hemorrhage, petechiæ, purpura hemorrhagica, herpes zoster, pemphigus, dermatitis herpetiformis, lupus erythematosus, keratosis blenorrhagica, and many others.

It now appears that in a few cases focal infection adequately explains certain cutaneous diseases in which up to now, to the best of my knowledge, that cause was not suggested for them. Such are the trichophytides, sporotrichosis, tularemia, and probably vaccinia and certain of the contagious exanthems.

It might be well at this time to apply rigid scientific criteria to the above groups, and to see to what extent focal infection is proven in one group, presumptive or likely in a second, and unlikely or improbable in the third.

In the proven group stand out syphilis, sporotrichosis and tularemia with their portals of entry in an injury, cases of systemic blastomycosis, the petechial and hemorrhagic lesions of bacterial sepsis, the trichophytides, scarlet fever, vaccinia, and the many extraordinary mutation forms of skin tuberculosis, including the sarcoid of Boeck, the deep tuberculosis of the hypoderm, and many of the so-called tuberculides. It may well be argued that systemic or blood-borne tubercle bacilli are difficult to determine, and that with all the evidence not at hand in every case, it

would seem improper, for example, to class lupus vulgaris in its many clinical forms, sarcoid tumor, lupus miliaris, and lichen scrofulosorum as examples of tubercle implantation from a remote focus. Admitting the validity of this argument, it is nevertheless true that the overwhelming preponderance of opinion favors the view that these are endogenous blood- or lymph-borne infections, and the weight of clinical evidence, together with some experimental proof, supports this view.

When we come to the tuberculides, however, we face a group of conditions which in part fit in with the concept of focal infections, and in part do not. It seems to be accepted that certain tuberculides are actually hematogenous tuberculous lesions. Bacilli have at times, with difficulty to be sure, been demonstrated, or occasionally animal inoculation has shown the lesions to contain bacilli. Others, on the other hand, are widely if not generally accepted as evidence of tissue changes due to tubercle toxin liberated from a tuberculous focus. To include such a group, providing the hypothesis of their nature is correct, in the class of focal infections, would necessitate a wider interpretation of our theory than we postulated at the outset.

In the interest of scientific accuracy, therefore, it would seem wiser to limit the term focal infection to those conditions in which systemic dissemination of pathogenic organisms occurs, and to place the group of toxic tissue reactions from remote foci, in a class which might properly be called *focal irritative processes*.

Following the researches of Jadasohn, Bloch, and their students, we may

now place in the group of proven focal infections the generalized dermatoses due to the hematogenous dissemination of mycelia and spores, originating in such local lesions as the kerionic ringworm. To these lesions the name of trichophytides has been given. The identification of this group and the demonstration of the entity as a systemic infection is a scientific achievement of considerable importance.

The petechial hemorrhages and purpura which are seen in the skin incident to bacterial endocarditis and to general sepsis, also fulfill the postulates of focal infections as do the rose spots of typhoid fever.

Scarlet fever is, of course, as good an example as is syphilis of a focal infection, if we accept the throat as the portal of entry of the streptococcus which produces the septic erythema. The weight of evidence also supports the view of a focal infection for the other contagious exanthems as well. Until we know more about the smallpox virus and the infectious agents of measles and chickenpox, however, we must place the entire group aside from scarlet fever and vaccinia as presumptive but not yet proven cases.

Sporotrichosis and tularemia are strikingly similar in their mode of onset as starting with lymph-borne infections, which occasionally develop septic manifestations. Both conform admirably to the criteria of focal infective processes.

Yaws in all probability fulfills the conditions of a focal infection, but until its epidemic character and method of transmission are better known, it is best not to include it in the proven focal infectious group at this time.

Although Rosenow has shown bacteria in some of the lesions of erythema multiforme, notably in erythema nodosum, and demonstrated similar strains in the tonsils and elsewhere, I do not believe the evidence at this time is sufficiently convincing to place this very large and varied group of cutaneous reactions with the proved cases of focal infection. The weight of clinical evidence, to be sure, in cases such as erythema nodosum in association with rheumatic fever, points to bacterial dissemination. However, it seems quite likely that many forms of erythema multiforme, perhaps the majority, are toxic rather than microbic processes. Many, indeed, very definitely are to be referred to such causes as foreign protein and drug reactions, thus establishing for them other etiologic factors than infective foci. While for the entire erythema multiforme group, foci of infection, therefore, as a cause do not fit, in isolated cases we may occasionally be dealing with hematogenous bacterial dissemination.

Toxins rather than infective organisms explain even more readily the urticaria group of dermatoses. These at one time may be due to local toxic irritations and at others to systemic intoxications, as from enteric protein sensitization or from toxins associated with gall bladder and hepatic disease. While frequent clinical evidence supports the view of foci of infection as the cause of urticaria, the local manifestation is never an evidence of systemic sepsis. It is a *focal irritative* rather than a focal infective process.

Herpes zoster is another disease probably definitely specific and due to an infective focus. The remote lesions

on the skin, however, can very properly be regarded as focal irritative rather than focal infective sequelæ. The immunity usually conferred by herpes zoster, moreover, does not fit in with the ordinary history of a focal infective condition where recurrence and chronicity are the rule. It stands out, however, as an admirable example of a change in a remote portion of the body dependent upon a focus of irritation.

A disease which may at some time be shown to be a focal infection, in which the evidence thus far is supported only by clinical evidence, is pityriasis rosea. The frequency of an initial plaque in this disease and the sudden explosion of satellite lesions support the view that we are dealing with systemic dissemination of an infectious agent from a primary plaque. My own experiments with this disease, extending over five years, while inconclusive, strengthen my belief that a specific blood-borne infectious agent is its cause.

Alopecia areata has been supported by many as an example of a focal infective disease. It is certainly true that the removal of carious and abscessed teeth has frequently resulted in the cure of this condition. Likewise, the uncovering of visual difficulties, sinus infection, and other foci of infection or irritation in the head, has resulted in spontaneous cure of the baldness. There is to my knowledge, however, no direct experimental evidence to show that alopecia areata can, in the strictest sense of the word, be a focal infection. If the preponderant number of cases cleared up upon removal of infectious foci, which in fact does not occur, the disease could at most be

placed, like herpes zoster, in the group of *focal irritative* processes

Many of our deductions as to the focal infective character of a disease are based first, upon the establishment of a focus of infection, and, second, upon the disappearance of the general process after the removal of the alleged focus. Both hypotheses are open to criticism. Most individuals can be shown to have some demonstrable focus of infection in the teeth, tonsils, gall bladder, appendix, prostate, or elsewhere. The finding of a focus is, therefore, only suggestive. Thus, if a tuberculous focus were found in a lymph node or tonsil in the presence of a cutaneous tuberculosis, the case would at once suggest the relationship between the two conditions, which might, however, be difficult of actual proof.

The clearing up of a systemic condition or of a dermatosis upon the removal of a focus of infection, moreover, has importance where bacteriologic proof is lacking, only when it occurs with great regularity, and only when other causes cannot operate to produce the same condition. Under these circumstances, focal infection may be assumed, but its ultimate proof still requires the demonstration of a pathogenic organism in both cause and result.

Where occasional cure of a dermatosis occurs upon removal of a focus, it is more than likely that this results from the relief of inhibitory forces which such a focus may exercise on general conditions, or it may be a response to general well being, resulting from the removal of the focus. These factors will explain the cases of lupus

erythematosus and of dermatitis herpetiformis, which occasionally clear up rapidly upon removal of infected foci. In both of these conditions the weight of evidence is against their being true focal infective processes.

It may properly be pointed out that occasionally the removal of a focus which, without doubt, is the causative factor of a dermatosis, is not followed by involution or even improvement in the focal infection. The demonstration and removal, for example, of a tuberculous lymph gland in the neck would effect little, if any, change in a resulting patch of lupus vulgaris, although it might well be a preventive measure against the development of new lesions. Irreparable tissue damage due to hematogenous germ dissemination cannot be followed by restitution when the source of the infection is laid bare and removed.

In conclusion, it may be emphasized that foci of infection play either a causal or a casual rôle in the etiology of many dermatoses, or their presence may have nothing whatever to do with the disease in question. Where the foci are *causal*, we are dealing with true focal infection as determined by blood-borne dissemination of the pathogenic organism from the focus to the satellite lesion. This occurs in a proven fashion in syphilis, cutaneous tuberculosis, certain tuberculides, the trichophytides, sporotrichosis, tularemia, systemic blastomycosis, vaccinia, and scarlet fever. A *casual* relationship occurs between foci and certain dermatoses with such frequency as to merit notice, and possibly to constitute a contributory etiologic factor in such conditions as erythema multiforme,

dermatitis herpetiformis, and alopecia areata

Finally, to the focal infective processes might well be added a group in which foci of infection play a direct rôle in the causation of satellite cutaneous lesions, in which pathogenic organisms are not present, but in which the tissue damage is apparently due to a toxic process. This occurs in herpes zoster, in some of the so-called toxotuberculides, in many of the multiforme erythemas, and occasionally in urticaria. This group might properly be referred to as *focal imitative* processes.

THE LYMPHOBLASTOMA GROUP

During the past twenty years I have had a most unusual opportunity of studying a very large number of cases of what formerly were termed the lymphadenoses of the skin. In this connection I have been singularly fortunate in the exchange of views with my late colleague, Waithin, who throughout his active life contributed much to the pathology of these conditions. In 1929 there were reported from my clinic by Keim twenty cases of various clinical types, of which ten came to autopsy. A great diversity of opinion exists as to the proper classification of diseases of the hemopoietic system. Those which are frequently found in the skin and occasionally occur there before their demonstration in other parts of the body are leukemia, both myeloid and lymphatic, lymphosarcoma, Hodgkin's disease, and granuloma fungoides. From our studies of this group of diseases we have come to the belief that genetically they are closely related, occasionally occurring

as combined pictures or changing from one clinical form to another.

From the clinical standpoint the most frequent cutaneous manifestation of the so-called lymphoblastomas occurs as a persistent scaling erythroderma. So frequently is a true lymphadenosis ushered in by a universal scaling dermatitis that the chronicity of this condition should always lead to suspicion of its grave nature. The condition may occur with or without changes in the circulating blood stream. In the majority of cases these are absent at the outset and develop only later in the course of the disease. In a few of our cases marked lymphocytic deviations in the blood occurred only shortly before death. In the large majority of cases a marked lymphadenitis is present, though not usually developing until the disease has been present in the skin for some months. I have, however, seen a few cases in which there was general lymphatic enlargement preceding the development of the erythroderma. Of greatest diagnostic import in determining the lymphoblastomatous nature of an erythroderma is the early biopsy. Even in the very early period the picture is quite characteristic—an infiltrate of lymphoblastic cells occurring in the upper portion of the corium either in clumps or as a sharp band-like infiltrate quite similar in its architecture to that seen in lichen planus. The biopsy of the lymph glands shows enormous hyperplasia and the same type of lymphoblastic cells as are seen in the skin. In two cases of an unusual type of cutaneous lymphatic leukemia I have seen an ordinary exfoliative dermatitis, unassociated with lymphadenitis and

with no unusual blood picture, entirely remit for several months, then reappear with associated lymph gland involvement, and finally remain in a state of chronic cutaneous lymphadenosis with the blood changes of a chronic lymphatic leukemia. In one case of cutaneous leukemia with marked changes in both the blood and lymph glands, spontaneous recovery took place after four years of observation, during which time the patient on several occasions was considered dangerously ill. Since this observation I have seen spontaneous recovery in a second similar case.*

In myeloid leukemia the cutaneous manifestations are considerably more rare. Quite apart from the cutaneous hemorrhages and purpura, one occasionally sees tumors of varying size and density, more particularly occurring on the face. Their appearance on the skin very occasionally antedates or is coincident with the first symptoms which lead to an examination of the blood and the establishment of the diagnosis. The tumors are pure myeloid in structure, and many exist only as transitory cutaneous manifestations of the disease. I have seen one universal type in which large tumors of a purplish-red color appeared all over the body, some of which ulcerated. The resemblance of this type of case to the entity, mycosis fungoides, is quite striking.

In Hodgkin's disease one may recognize on the skin the so-called essential types of eruptions. These take the

form of definite nodules. The architecture of the latter conforms exactly to that of the pathologic picture seen in the lymph glands. The so-called non-specific lesions occurring in Hodgkin's disease take the form of prurigo-like nodules and excoriations and pigmentation. These are alleged to be toxic reactions rather than examples of true cutaneous Hodgkin's disease.

In at least one case, however, in which prurigo-like nodules occurred, I was able to demonstrate in the nodules very definite pathologic architecture typical of the disease.

The pigmentation seen in Hodgkin's disease is sometimes of a very bizarre nature. I have at present under observation a young man who was admitted for an ex-foliative dermatitis which rapidly cleared up on topical remedies. He returned to the hospital less than a month ago with a zone or band of deep brownish pigment extending around the waist and onto the upper portion of the thighs. There was also hyperpigmentation of the axillæ and sufficient thickening of the skin to suggest at least, a diagnosis of acanthosis nigricans—a pigmentary disorder discovered by Pollitzer many years ago and shown by him to be a frequent accompaniment of abdominal neoplasm. In addition to the pigmentation there was marked enlargement of the inguinal and axillary lymph nodes. A biopsy taken from these and from the overlying thickened skin showed typical early Hodgkin's disease.

With regard to lymphosarcoma, the cutaneous manifestations are extremely varied. One may have, as in leukemia, a scaly erythroderma, apparently benign at the outset and leading to

*Since this article was written the first patient has returned to the hospital with a relapse of the skin condition and with glandular enlargement, after a remission lasting over four years. (Author)

the diagnosis of simple exfoliative dermatitis from one cause or another. Subsequently a marked enlargement of the lymph nodes leads to the suspicion of the lymphoblastomatous nature of the eruption, and the biopsy, both skin and lymph node, readily establishes a diagnosis of small or large round-celled sarcoma. In the late stages of this condition actual metastatic nodes in the skin may occur in large numbers in various parts of the body. In other cases lymphosarcomatous nodes may appear in various parts of the otherwise normal appearing skin, to be followed at a later time by the generalized involvement of the lymph nodes. The picture of the erythrodermatous type is indistinguishable clinically from leukemia and from occasional cases of Hodgkin's disease.

I have before referred to the occasional combination pictures which are seen in these various conditions. So closely may they simulate each other that a clinical diagnosis must on occasion be changed from time to time during the course of the disease. Two cases will serve to illustrate this point. In one, definite lymphosarcomatous nodes were removed from the skin of a young boy who at the time showed little or no change in his blood. He later showed severe hemorrhages into the skin and hemorrhages from his mucous membranes, following which he developed a rapidly fulminating type of lymphatic leukemia from which he died. A second case which I still have under observation is that of an elderly man with multiple lymphosarcomatous nodes in the skin and lymph glands in whose blood at this time there are changes suggesting leukemia.

Many years ago there was demonstrated before the Dermatological Section of the Academy (New York) a patient in whom at the time it was believed both leukemia and granuloma fungoides were present. The case which I cited before of a young boy who died of myeloid leukemia in whose skin a large number of large ulcerative nodules occurred is, I believe, the analogue of this condition.

An interesting question arises in connection with those cases of lymphoblastoma in which a scaly erythroderma of an innocent type antedates the more serious phase of the disease. The suggestion in this type of case is that the cutaneous insult may be a primary factor in the activation of the lymphadenosis. In cases biopsied during the early period there may be no suggestion of a lymphoblastomatous infiltrate. While the majority of the cases are undoubtedly lymphadenoses from the outset, it is nevertheless a tenable hypothesis that in a few cases at least the lymphadenosis may be secondary to a prolonged skin insult. The analogy, at least, is present as regards occasional infection and acute lymphatic leukemia.

My own studies have convinced me that the lymphadenoses are reflected in the skin in three different ways. First and perhaps more rarely one may find in the incidence of lymphadenotic blood pictures, the cutaneous expressions as infiltrations and tumors, together with hyperpigmentation. These are true metastatic lesions. Second one finds pictures in which the cutaneous lymphadenotic infiltrations antedate the chronic involvement of the blood and lymph glands. In this group are found large numbers of cases of exfoliative

dermatitis of great chronicity, as well as isolated tumors and infiltrations. The third group includes particularly scaly erythrodermas and occasionally also localized infiltrations in which transitory deviations from the normal are found in the blood stream, together with characteristic hyperplastic changes in the lymph nodes. In this group occasional recovery may take place with complete restitution even after several months or years. In such cases I believe the skin pathology rather than reflecting systemic changes, may by continuous insult act as a causative factor in the production of secondary lymphadenotic changes which simulate closely the typical primary cases.

The group of lymphoblastomas illustrate admirably the cutaneous manifestations of systemic disease. They represent a very small although impor-

tant group which serves merely as a text upon which to elaborate the theme under discussion. One might with equal profit, if the time permitted, discuss the cutaneous manifestations of glycosuria, the unique changes in the skin incident to the disorders of fat metabolism such as occur in xanthoma, the atrophic changes of arteriosclerosis and senility, the remarkable changes in the integument with endocrinous dysfunctions, and the subject of the skin as a reflector of emotional states. These, and many others, could each be taken as a text to illustrate that, apart from its protective function, its thermostatic control, and its secretory and excretory functions, the skin admirably reflects and intimately takes part in many, if not most, of the morbid processes of the body.

Malignant Thymoma

of Reticulum-Cell Type With Pressure on the Left Lung, Trachea, Esophagus, Left Phrenic and Left Recurrent Laryngeal Nerves, and With Metastases to the Glands of the Left Side of the Neck; Importance of Biopsy for Differential Diagnosis of Cervical Lymphadenopathies*†

By LEWELLYS F BARKER, M D, F A C P, *Baltimore, Md*

THE patient selected by Professor Pincoffs to be discussed by me this afternoon illustrates very well not only the importance of making a general diagnostic survey, but also the great diagnostic help that may be derived from bioptic examination of a lymph gland when there is enlargement of the glands in the neck. Though we make it a rule to select, ordinarily, for demonstration at these clinics, cases of the more frequently encountered maladies of interest to the general practitioner, we are breaking that rule today in order to show you one of the rarer pathological states that offer certain difficulties in exact diagnosis.

CLINICAL HISTORY

The patient, Thomas M., a white huckster, aged 40, was admitted to Ward G of this hospital (service of Dr Harry M Stein) on October 27, 1931, complaining of hoarseness, cough, pain and swelling of the left neck, and loss of weight.

Present Illness About three months ago

*Clinic to physicians at the University of Maryland, November 19, 1931.

†Received for publication, November 24, 1931.

the patient picked up a heavy basket of fruit and, under the strain, suddenly felt a rather severe pain in the left neck. This pain disappeared, however, when he set the basket down. He was surprised when placing his hand upon the region in which he felt the pain to find a lump in the left neck. At about the same time he began to cough and to raise some sputum (without blood), he noticed also that his voice was becoming hoarse. One week after lifting the weight, he noticed that he was having pains radiating from the lump in the neck into the chest, and these gradually grew worse. He applied to the hospital dispensary for examination, and, after several visits and an x-ray examination of the chest, it was supposed that he had tuberculosis of the left upper lobe and of the lymph glands of the neck and he was sent to the tuberculosis department of the City Hospitals for treatment, though one of the examiners in the dispensary felt confident, even before x-ray examination of the thorax, that there was a tumor mass in the mediastinum. As no tubercle bacilli could, however, be found in the sputum on repeated examinations at the City Hospitals, a lymph gland was excised from the posterior triangle of the neck for diagnostic purposes, it was found to be non-tuberculous and it was thought to be sarcomatous. The patient was discharged by Dr Charles C Habliston and told to return to the dispensary here for further observation and for radiotherapy. As he continued to

lose weight and to remain hoarse, he was admitted to Ward G on October 27th

Previous History Except for measles in childhood and an attack of gonorrhea fifteen years ago, the patient has always been healthy. He has worked at various jobs. He apparently has never taken enough food for he has always been below ideal weight. He smoked one package of cigarettes a day up to the time of the present illness, and it was his custom to drink one quart of whiskey per week until seven or eight months ago. There has been no excess in the use of tea and coffee and he has not made use of drugs until needed for relief of pains in the present illness.

Family History The patient is married and his wife and two children are well. The family history has no bearing upon the patient's condition.

Physical Examination The patient's height is five feet, three inches, and his weight is 111 pounds, so he is a little more than fifteen pounds under calculated ideal weight. Since admission to the hospital, his temperature has varied between 99.4° on admission and 101.6° as a maximum. His pulse rate has varied from 80 to 110, and his respiratory rate from 20 to 25 per minute. He is of asthenic habitus.

In the head, no abnormal findings were observed except marked dental caries, gingivitis and a little hyperemia of the pharynx. No tumor masses could be made out in the nose or throat. The nasal septum was slightly deflected to the left. The voice was very hoarse and of low pitch.

In the neck, the thyroid was not enlarged. There was no tracheal tug. The trachea was displaced to the right and in the left supraclavicular fossa was a mass of rather soft lymph glands, more or less matted together (figure 1). The glands along the edge of the sternomastoid muscle were also enlarged on the left side. In the right side of the neck there was a wen about the size of a walnut.

The thorax was long and thin and the epigastric angle acute. There was some dilatation of the veins in the front of the left thorax and in the left side of the neck, the left half of the chest looked somewhat flatter than the right.

On respiration, there was distinct lag and lessened movement of the whole left chest as compared with the right and, on palpation, there was greater vocal fremitus over the right lung than over the left. On percussion, there was marked retrosternal dullness, and flatness over the left upper lobe, both in front and behind, the dullness extending behind downward to the level of the spine of the third thoracic vertebra and in front down to the fourth intercostal space and some four cm lateralward from the left parasternal line. On auscultation, aside from occasional sibilant and sonorous râles in both lungs, nothing was made out except relative suppression of the breath sounds in the left upper lobe, probably due to atelectasis. No pleural friction was heard.

The heart seemed to be of approximately normal size and there were no heart murmurs.

The abdomen was retracted and the liver was palpable one or two fingerbreadths below the costal margin. The tip of the spleen could not be felt.

Examinations of the nervous system (except for evidences of pressure on certain intra-thoracic nerves) were entirely negative and the psyche was clear.

Laboratory Tests *Sputum* Mucopurulent. No tubercle bacilli. No blood. Many streptococci.

Blood RBC, 3,970,000 to 4,340,000, on different counts. Hemoglobin, 80 per cent on admission, since reduced to 55 per cent. White cell count has varied between 11,800 and 15,280. Differential count: Polymorphonuclears, 75 per cent to 78 per cent, small mononuclears, 18 per cent to 23 per cent, large mononuclears and transitionals, 7 per cent to 11 per cent. Wassermann and Kolmer reactions, negative.

Urine Specific gravity, 1010 to 1015, negative for albumin and sugar, an occasional cast seen, no pus cells, occasional red blood corpuscle present, phthalein output 75 per cent in two hours.

Röntgenological Report (Dr Henry J Walton) Mediastinal tumor extending into the left side of the chest, situated more anteriorly than posteriorly. Atelectasis of the upper lobe of the left lung. Elevation and fixation of the left diaphragm. Dislocation

of the esophagus and trachea to the right with some narrowing of the lumen of the esophagus. Heart small and apparently rotated. Slight hypertrophic osteoarthritis of the thoracolumbar spine. Sacralization of fifth lumbar vertebra. No evidence of tumor metastases in the bones. (Figure 2)

Reports of Specialists *Nose and Throat examination (Dr Looper)* Paralysis of the left arytenoid and complete paralysis of the left vocal cord, probably due to pressure on the left recurrent laryngeal nerve.

Biopsy of Cervical Lymph Gland On request of the internist, the hospital surgeon, Dr Shipley, removed a lymph gland from the left side of the neck for microscopic examination. The histological study was made

by Dr Hugh R. Spencer who made the following report:

"Capsule of lymph gland intact. On section, node is grayish white and appears to be cellular. One small area is yellowish and necrotic. On microscopic examination, the lymphoid tissue is replaced by actively growing tumor cells, which vary in morphology, some of them being round and others polyhedral, while those in relation to the blood vessels are somewhat columnar in shape and lie at right angles to the vessel walls. Many of the nuclei are hyperchromatic and mitotic figures are numerous. The blood vessels are poorly formed and, in some areas, tumor cells are in direct contact with the blood. There is some alveolation of the tumor but,



FIG. 1 The mass of lymph glands in the left supraclavicular fossa is visible, as well as the scar following the removal of a gland for histological examination. The small mass in the right side of the neck is a sebaceous cyst. The dilatation of the veins below the left clavicle can be seen.

in general, the arrangement is perivascular

"Impression The tumor is a sarcoma of the reticulum cell type, different from the usual type of reticulum cell lymphosarcoma in the arrangement of cells and in the vascularity of the tumor The thymus gland should be considered as the probable site of the primary tumor"

Course in the Hospital The patient's general condition has been closely watched by the interne, Dr M Cohen, and it has not undergone any marked change during his three-weeks' stay in the hospital The blood pressure has continued low, varying between 86 and 106 systolic and between 48 and 68 diastolic The secondary anemia has been increasing so that the hemoglobin is now down to 55 per cent The patient is holding his weight very well and has a fairly

good appetite He still tires very easily on exertion and has some pain in the left neck and in the upper chest

DISCUSSION OF THE CLINICAL FINDINGS

The Mediastinal Mass This space-occupying mass in the upper anterior mediastinum is causing pressure upon the left bronchus and left upper lobe, which has resulted in atelectasis There may be some actual infiltration of the lobe by the tumor mass The situation of the mass points to the thymus gland as a source of the pressure rather than to the lymph glands at the



FIG 2 Roentgenogram of the chest

root of the left lung. There is no evidence that the mass is a substernal thyroid. This mass has dislocated the trachea to the right and has caused pressure upon the esophagus. It has also pressed upon the left recurrent laryngeal nerve, causing paralysis of the left vocal cord. It has compressed the left phrenic nerve and has caused paralysis of the left half of the diaphragm. Whether the tachycardia is due to pressure upon the vagus with partial loss of vagal inhibition is not certain.

It is evident that we are not dealing with a simple hyperplasia of the thymus but with a true tumor growth.

The Cervical Lymphadenopathy

You will recall that the patient's first symptom was pain in the left neck and the finding of a swelling in that region. On examination at the hospital dispensary, and, later, in the hospital itself, the swollen neck was found to depend upon enlargement of the supraclavicular lymph glands and of the lymph glands along the sternocleidomastoid muscle. One of these was removed by biopsy at the City Hospitals and found to be non-tuberculous, though the sections suggested sarcoma. Another gland removed in the University Hospital was found to be the site of definite metastatic tumor growth.

The x-ray findings in the mediastinum of tumor, the evidences of metastases in the glands of the neck, and Dr Spencer's histological studies make it fairly clear that the site of the primary tumor is the thymus and that the histological character of the tumor is of the reticulum-cell type. In using the term "reticulum" Dr Spencer had in mind the reticular histiocytes and

the perivascular mesenchymal cells rather than the reticular epithelium.

Whether this tumor should be regarded as sarcoma or as carcinoma is a question that merits discussion. Much help in classification in the great group of lymphoid tumors may ultimately result from more general patronage of the "Lymphoid Tumor Registry" of the Army Medical Museum in Washington.

Dr Spencer leans to the view that the neoplasm in our patient should be designated a "lymphosarcoma" and in this assumption he would be in accord, I believe, with one of our best American authorities on neoplasms, Dr James Ewing of New York. The character of the cells of the tumor and the vascularity of the growth are the points upon which this diagnosis of lymphosarcoma is based. Warthin of Ann Arbor would probably have placed the tumor in the group that he designated "aleukemic lymphoblastomas," a group that contains round-cell sarcoma, lymphosarcoma, lymphoma, and lymphadenoma, and he inclined to the view that many tumors reported as originating in the thymus have probably been primary in the mediastinal lymph nodes.

On the other hand, most will agree that both the cortical and the medullary cells in the thymus, including some of the reticulum cells, are originally of epithelial origin. Moreover, the fact that metastasis is through the lymph channels to the lymph glands rather than through the blood is further evidence in favor of carcinoma rather than of sarcoma. There are, therefore, many who would place this tumor in the carcinoma-

tous group The French writers lean to carcinoma, the German authors to sarcoma when they describe thymic tumors of this sort Perhaps we will do best to compromise, as Schridde does, and simply speak of a "malignant thymoma," not committing ourselves definitely as to whether the neoplasm is of mesoblastic or of epithelial origin The marked polymorphism of the cells, emphasized by Ambrosini is one of the chief characteristics of these thymic tumors and is very obvious in the microphotographs of the sections of the tumor of the patient before you (Figures 3 and 4)

The Anemia This anemia is clearly of the secondary rather than of the primary type and it is probably related to the tumor growth itself and the

toxins produced by the neoplasm There is nothing in the blood suggestive of Hodgkin's disease, of leukemia, or of other blood dyscrasias

The Undernutrition This man is fifteen pounds under calculated ideal weight and he reports that, during the past three months, he has lost a good deal of weight He states, however, that he has never been overweight and that is not surprising since he is of asthenic habitus

The Weakness This patient has complained much of his physical weakness and muscular fatigability His eyelids do not droop, however, and his jaw muscles do not tire on chewing beefsteak We must keep a close watch upon the muscular functions since myasthenic states, indistinguishable from myasthenia gravis pseudoparalytica.

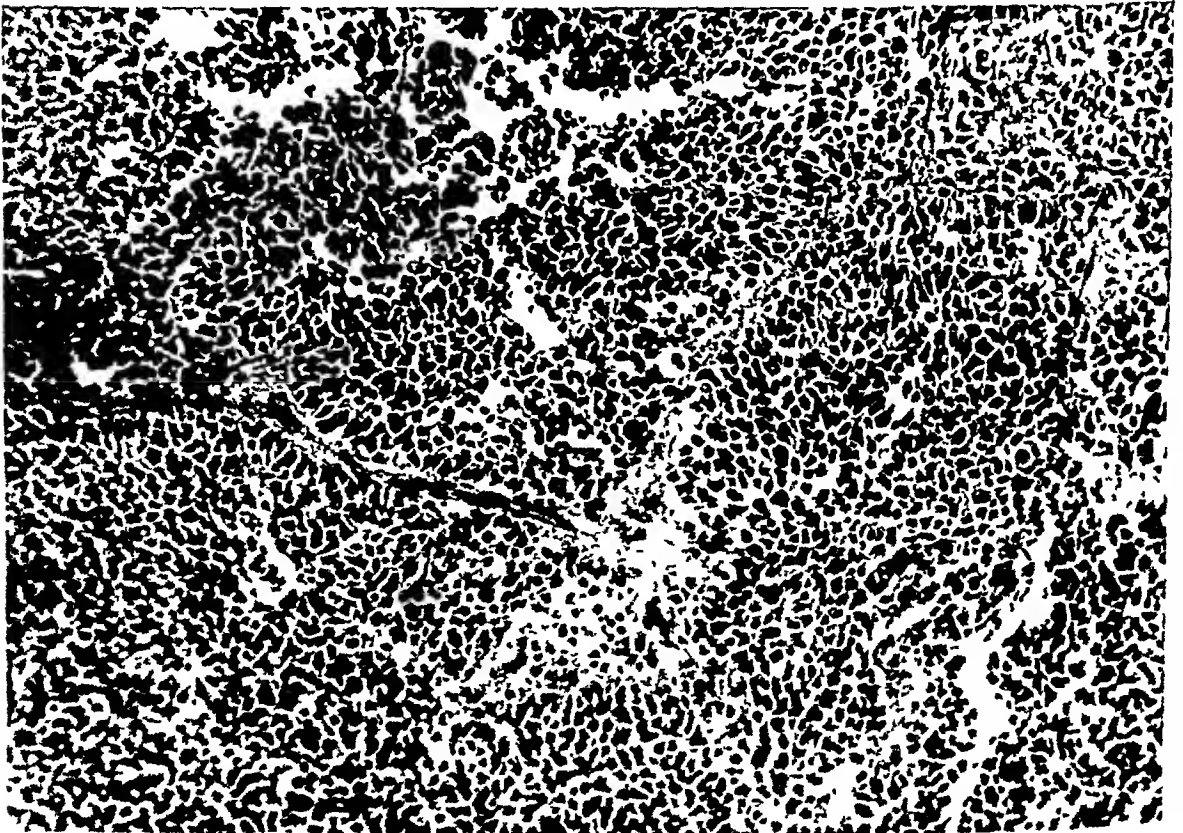


FIG. 3. Section of excised lymph gland as seen under the low power of the micro-

have occasionally developed in patients exhibiting tumors of the thymus. In one of these reported by Mandelbaum and Celler (1908), the thymus tumor was described as a "perilymphatic lymphango-endothelioma", in other instances, the tumor was described as lymphosarcoma (Hun)

The Dental Caries Though this patient has marked dental caries and some gingivitis, it is not probable that the trouble with the teeth and gums stands in any relation to the other clinical findings, except possibly to the secondary anemia to which it could have been a contributing factor

DIFFERENTIAL DIAGNOSIS

We have had a clear demonstration of the fact that enlargement of the lymph glands in the neck may, for a

time, puzzle the diagnostician. Thus, this patient was under observation during several visits at the hospital dispensary and was finally sent to the City Hospitals because he was believed by some to be suffering from tuberculosis of the lymph glands and of the left upper lobe, and by one of the examiners to be suffering from mediastinal tumor. Biopsy has finally proven that without doubt we have to deal with metastatic neoplasm of the cervical lymph glands and this fact (together with the x-ray findings and the general clinical study) points to the thymus gland as the probable primary site of the neoplasm.

Any space-occupying mass within the mediastinum may give rise to a variety of clinical phenomena, for we must not forget that increased pres-

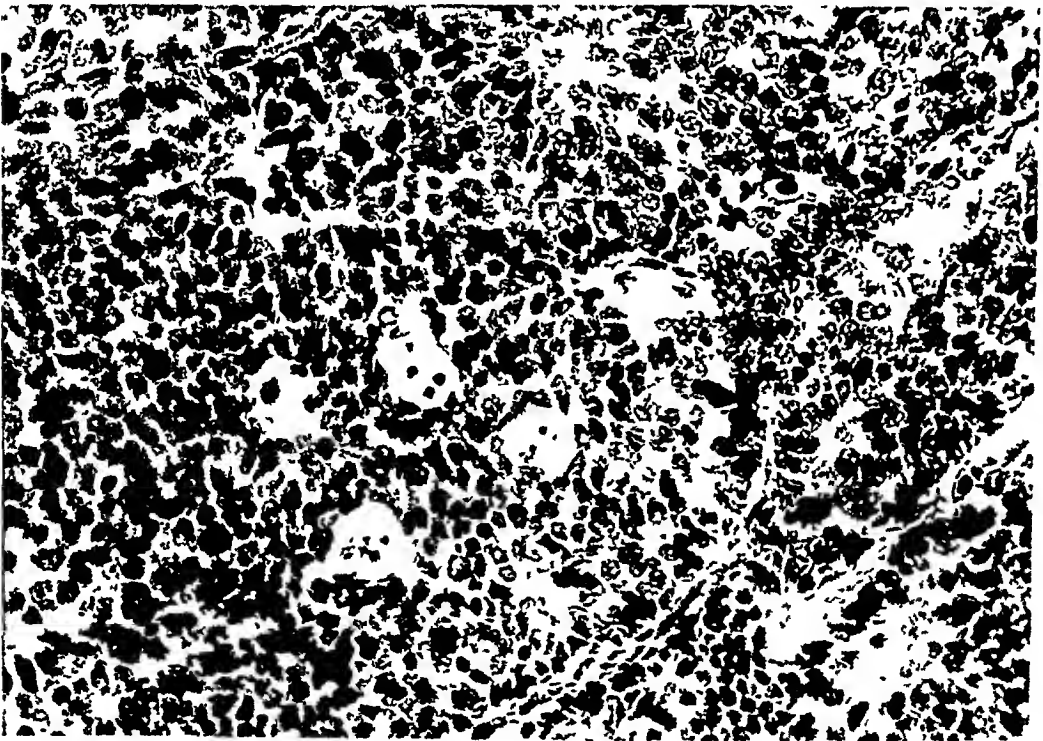


FIG 4 Section of the excised lymph gland as seen under high power magnification

sure within the mediastinum can affect any one or several of a group of very important structures, including the large blood vessels, the heart, the trachea, the esophagus, the thoracic duct, the thymus gland, the lymph glands at the root of the lungs, and several very important nerves including the vagus and its branch, the recurrent laryngeal, the phrenic, and the sympathetic trunk. Symptoms and signs of space-occupying masses within the mediastinum are usually due to compression of one or another of these structures. As a rule, it is the large veins that are first compressed, especially the superior vena cava, and, accordingly, dilatation of the veins of the chest and of the neck is an early symptom in most cases. In this patient, it is surprising that there has been no greater compression of the veins than has occurred, though that there is already some collateral circulation is obvious.

Most space-occupying masses within the mediastinum are true tumors but other processes may simulate tumors.

Of the *primary tumors of the mediastinum*, thymus tumors, tumors originating in the lymph glands, thyroid tumors, and dermoid cysts, are the most common.

Of the *secondary tumors of the mediastinum*, it should be remembered that metastases into the lymph glands of the mediastinum can give rise to space-occupying masses within the chest; for example, we may find them in association with carcinoma of the stomach, of the lung, or of the breast. Carcinoma of the esophagus or of a bronchus can also through metastases give rise to such masses.

Inflammatory masses in the mediastinum may be due to tuberculous abscess, especially when secondary to caries of the cervical spine.

Aneurysm of the aorta or of a subclavian artery can also give rise to a space-occupying mass in the mediastinum.

It is an interesting fact that the majority of patients with true mediastinal neoplasms are in early or middle life, rather than in later life, though they may occur at either period.

Among the *compression phenomena* met with, when there is a space-occupying mass in the mediastinum, certain *subjective symptoms* are common —

- 1 An obstinate, dry cough, often metallic in type, and sometimes occurring in paroxysms.
- 2 Hoarseness and bitonal voice, due to pressure upon the left recurrent laryngeal nerve and the effect of this upon the left vocal cord.
- 3 Dysphagia, due to pressure on the esophagus.
- 4 Pains, due to pressure upon the intercostal nerves, pains that radiate into the neck and the walls of the thorax and, sometimes, into the arms.

Though these subjective symptoms are usually more or less prominent, there are also variable *objective findings*, which may include

- 1 Swelling of the superficial veins, limited to the upper half of the body and often more marked on one side than on the other.
- 2 Swelling of the whole head and neck due to edema (so-called "Stokes' collar"), not present in this patient.

- 3 More or less marked cyanosis
- 4 Changes in the lungs, due to infiltration of the tumor or to pressure upon the lung or a bronchus with production of atelectasis
- 5 Chylous hydrothorax, due to pressure upon the thoracic duct (not present in this patient)
- 6 Characteristic findings on x-ray examinations of the thorax
- 7 Evidences of metastases in regional lymph glands

Even before the biopsy of the cervical lymph gland, it was possible to rule out many of the affections that might otherwise have had to be considered. Thus, *sphilis* was ruled out by the negative serology, *tuberculosis* was made improbable by the absence of tubercle bacilli in the sputum, *leukemia* was ruled out by the negative blood picture, *Hodgkin's disease*, of course, had to be thought of and particularly, because in the blood there was a rather high count of the large mononuclears and transitionals, but there was no eosinophilia, the patient had no pruritus, and the lymph gland enlargement was restricted to the left neck, and primary *tumors of the nasopharynx* were eliminated by careful inspection of the nose and throat.

The great value of the x-ray examination of the thorax and of the biptic examination of the lymph glands of the neck are well-illustrated in this patient. Thus, the x-ray examination revealed the space-occupying mass and its site in the upper anterior mediastinum, pointing to probable origin in the thymus gland. The biopsy of the lymph gland proved that we were dealing with a neoplastic process and that the histological character of the neo-

plasm was very suggestive of a thymic origin. *I cannot emphasize too strongly the desirability, in doubtful cases, of resorting to biopsy of a lymph gland for differential diagnostic purposes.* The procedure is a very simple one and involves practically no risk to the patient. The results, for diagnosis, are, in many cases, positively decisive.

DIAGNOSTIC CONCLUSIONS

From what I have said, we are justified, I believe, in making the following multi-dimensional diagnosis:

- 1 Malignant thymoma of reticulum cell type, causing pressure on the left lung, the left phrenic nerve, and the left recurrent laryngeal nerve, dislocating the trachea and the esophagus and giving rise to metastases to the lymph glands of the left side of the neck
- 2 Undernutrition, 15½ pounds
- 3 Secondary anemia (red blood cells, 3,970,000, hemoglobin, 55 per cent, with moderate leucocytosis, 11,800-15,280)
- 4 Febrile reaction, temperature 99.4°-101.6°, perhaps dependent upon the neoplasm itself, perhaps due to acute pharyngitis or to bronchitis of streptococcic origin
- 5 Slight hypertrophic osteoarthritis of the thoraco-lumbar spine
- 6 Dental caries and gingivitis
- 7 Sebaceous cyst in the right neck

PROGNOSIS

As the patient has been sent back to the ward, we may, in his absence, discuss the prognosis.

Though temporary improvement can be brought about by therapy, the pros-

pect in a case of this sort, judging from past clinical experience, is that exitus will occur within twenty-one months of the time when the first symptoms appeared, or earlier

TREATMENT OF THE PATIENT

In my opinion, there is no indication for surgical intervention in this patient. Attempts to remove the intrathoracic tumor are unjustifiable. The risk from the operation itself would be very great, in the first place, and, in the second place, there is no probability that such surgical intervention would prolong life. Nor is there any advantage to be derived from removal of the lymph glands of the neck, except for diagnostic purposes.

The best therapeutic methods of intervention at our disposal are deep roentgenotherapy and radium therapy. It is possible that we may be able to reduce the size of the mass within the thorax and also the size of the enlarged lymph glands of the neck by such treatment. Of course, everything should be done, in addition, to build up the general health and strength of the patient by diet and by suitable hygiene. Unhappily, we must recognize that any favorable results of therapy will be of but temporary duration. Later on, it will be the duty of his medical attendants to ensure a gentle and easy death by the now well-known methods of inducing euthanasia in the victims of hopeless neoplastic disease.

SELECTED REFERENCES

- AMBROSINI, G. De l'épithéliome du thymus. These de Paris, 1894, No 344, 60 pp.
- v BERGMANN, G. Die Erkrankungen des Mediastinum. In Handb d inn Med (v Bergmann and Staehelin), 2 Aufl, Berl, 1928, II, pt 1, 637-672.
- EWING, J. The thymus and its tumors. In *his* Neoplastic diseases. Phila, W B Saunders Co, 3 ed, 1928, 966-977.
- HALPERN, F and POPPER, H. Ueber einen Fall von Myasthenie bei einer lympho-epithelialen Geschwulst der Thymusdruse. Ztschr f d ges Neurol u Psychiat, Berl, 1931, cxxxii, 296-310.
- HUN, H. Myasthenia gravis, with a report on the autopsy by G Blumer, together with a report of the microscopical examination of the tissues by G L Streeter. Albany Med Ann, 1904, xxv, 56-69, 3 pl.
- LEVIN, I. Lymphoma malignum (Hodgkin's disease) and lymphosarcoma. Pathogenesis, radiotherapy and prognosis. Jr Am Med Assoc, 1931, xcvi, 421-426.
- MANDELBAUM, F S, and CELLER, H L. A contribution to the pathology of myasthenia gravis, report of a case with unusual form of thymic tumor. Jr Exper Med, 1908, x, 308-328, 3 pl.
- MATTI, H. Physiologie und Pathologie der Thymusdruse. Ergebn d inn Med, 1913, x, 1-144.
- RABINOVITCH, A M. Zur Diagnostik der Thymome. Fortschr a d Geb d Rontgenstrahlen, 1913, xlii, 71-75.
- SCHRIDDE, H. Bosartige Thymusgeschwulste. In Aschoff's Pathol Anat, 5 Aufl, II, 188-189.
- SPIES, J W. "Lymphosarcoma" of the neck. Surg, Gynecol and Obst, 1931, lvi, 815-824.
- THIROLOIX, J, and DEBRÉ, R. À propos d'un épithélioma du médiastin antérieur, essai de classification des tumeurs cancéreuses de la loge thymique. Arch de méd expér et d'anat path, Par, 1907, xix, 668-696.
- WARTHIN, A S. The pathology of thymic hyperplasia and the status lymphaticus. Arch Pediat, NY, 1909, xxvi, 597-617. Also Diseases of the thymus. In Mod Med (Osler and McCrae), 3 ed, Phila, 1927, v, 428-460.

The Management of Severe and of Atypical Hyperthyroidism*

By FRANK H. LAHEY, M.D., *Boston, Mass.*

WE wish to call attention to two thyroid states concerning which very little appears in the literature, and both of which possess very serious possibilities of fatalities unless properly appreciated and properly managed. The first is the patient with very severe hyperthyroidism bordering upon the so-called thyroid crisis, and the second is the state which we have termed apathetic thyroidism.

SEVERE HYPERTHYROIDISM

Patients with exophthalmic goitre apparently have the faculty of not infrequently leading their medical advisors into a false sense of security. This is perhaps due to the fact that patients with this disease are notably optimistic. Clinically this feature of optimism is very striking in hyperthyroidism. We have often said that so-called nervous states of thyroid origin differ from those of psychic or neurotic origin in that the patient with hyperthyroidism insists that he can do things in the way of physical effort, but actually cannot, while the latter one says he cannot do things, but actually can. The fact that patients even with quite

severe thyroidism are able to be up and about and to maintain at least in some measure their activity, tends also to lead one to the feeling that there is no real hurry about them, and that active measures may be put off from week to week, with the possibility of the appearance of a remission, which may, of course, be prolonged into a permanent one and complete relief from the disease.

Based upon an experience now with nine thousand three hundred thyroid operations, we have had it impressed upon us that patients with severe hyperthyroidism are always upon the verge of a thyroid crisis and require the addition of only seemingly slight factors to so intensify their hyperthyroidism that they progress into a real thyroid crisis with its extreme ceaseless agitation, delirium, vomiting, diarrhea and uncountable tachycardia.

In patients with advanced grades of hyperthyroidism we have seen toxicity intensified to a crisis by the occurrence of a superimposed infection such as an ulcerated tooth and its removal. Frequently it has followed the occurrence of follicular tonsillitis, acute appendicitis and acute influenza infection. We have seen an acute thyroid crisis appear following a simple perineorrhaphy with a general anesthetic,

*Scheduled for presentation at the Baltimore Meeting of the American College of Physicians, March 26, 1931

an operation for gall stones, and we have had patients in whom serious thyroid reactions have followed simple tonsillectomy with a general anesthetic. We have likewise seen patients with severe hyperthyroidism progress into thyroid crises with no apparent inciting causes.

We have learned in dealing with such a large number of these cases that if these patients are permitted to progress into the stage of intense thyroid intoxication where they are delirious, vomiting, overactivated and with exaggerated heart rates, a very large percentage of them will die in spite of all measures to get them out of their critical state. Based upon our own experiences with these critical states, we wish to call attention to the fact that the time to instigate active measures against thyroid crises is before they have actually occurred, and that if active measures are instituted at this stage, a majority of the patients will be kept out of the crises and can be gotten into such improved states that active measures such as surgery can be undertaken with relative safety and the course of the disease quite definitely checked.

One should have in mind that every patient with intense hyperthyroidism may at any time pass into a thyroid crisis, and attention should be directed toward detecting the earliest possible indications of an impending crisis, such as sudden and persisting increases in pulse elevation, definite increases in activation, particularly when associated with changes in the mental state such as irrationality. Perhaps the most certain forerunner of thyroid crisis is vomiting, as, if it persists with its de-

hydration and emotional upset, a thyroid crisis, if not already present, is quite likely to occur. Diarrhea is tolerated much better than is vomiting, but is not to be neglected as a possible warning of an impending thyroid crisis.

It is at the time that these early premonitory signs occur that active measures against the intensifying hyperthyroidism must be undertaken if we wish to save the lives of these seriously threatened patients. If these patients have not been receiving iodine, it should be given in the form of Lugol's solution by mouth, ten drops three to four times a day, by rectum if not tolerated by mouth, and if it is not possible to administer it by mouth or rectum, we have found that fifty minims can be put in 750 cc of salt solution and administered by hypodermoclysis.

Patients with an impending thyroid crisis are usually in a state of marked overactivation which must be controlled if their organism is to be protected against their own hypercombustion. This can best be done, in our experience, with morphia or sodium amytal. We have never used avertin, but if a serious case presents itself with wild activation and delirium, we are planning to employ it if morphia and sodium amytal do not quiet the individual. It is to be recalled that patients with intense hyperthyroidism tolerate good-sized doses of morphia, and it must be given until its effect is obtained or respirations reach a dangerously low level.

Of measures to combat impending thyroid crises, salt solution and glucose are, in our experience, the most strik-

ingly valuable. Those patients either in crises or on the verge of thyroid crises should receive a minimum of 3000 c.c. of salt solution with 150 gms of glucose every twenty-four hours until their urgent symptoms have diminished as evidenced by a drop in pulse rate, diminution in excitement, return of mental clearness and a disappearance of vomiting and diarrhea.

Just how glucose and salt solution protect these patients against the rapidly destructive effects of intense thyroidism, we cannot say. Whether it protects them by increasing the glycogen reserve in the liver, or whether it restores water balance and protects the organism against hypercombustion by providing a material which is readily burned, we do not know. We do know that the administration of salt solution and glucose in reasonably large doses has been the salvation of many patients in severe post-operative thyroid reactions and in patients already in severe thyroid crises when coming to the Clinic, and that its employment as suggested above on the slightest warning of an impending crisis has prevented many patients from progressing into a serious thyroid crisis, and so undoubtedly saved their lives.

We feel sure from our experiences with these cases that it is a mistake not to have them operated upon as soon as one reasonably can after recovery from the crisis or threatened crisis, as they are still intensely toxic and capable of again being precipitated by another infection into another crisis. We believe that any patients who have hyperthyroidism of such a severe degree that they are in danger of a crisis, should be definitely freed from that

toxicity as quickly and as completely as possible by such an active measure as subtotal thyroidectomy.

APATHETIC THYROIDISM

We have from time to time written about what we have called apathetic thyroidism, and I am anxious to present this subject to several different groups of medical men because I feel sure that its diagnosis is often overlooked and certainly its seriousness often underestimated.

The signs of so-called apathetic hyperthyroidism are quite contradictory to those of typical hyperthyroidism or exophthalmic goitre which is of the type which we have called activated in contradistinction to this inactivated or apathetic type.

Activated or typical hyperthyroidism tends to occur in the majority of cases, in patients up to forty or fifty years of age. Apathetic hyperthyroidism tends to occur in patients above forty to fifty years of age. Activated hyperthyroidism is characterized by quite definite eye signs, not always exophthalmos but usually stare. The eyes in apathetic hyperthyroidism are usually not characterized by exophthalmos, are in repose, and not staring. The thyroid of activated hyperthyroidism is particularly apt to be larger than normal and of a definite firm hyperplastic character. The thyroid in apathetic hyperthyroidism tends to be smaller than that which is found in activated hyperthyroidism, although in these conditions the size of the gland may be reversed. Pulse rate in activated hyperthyroidism tends to be high and of a striking character, snapping and full; while the pulse rate of apathetic hyperthyroid-

ism tends to be relatively low, one hundred and twenty or under, and not particularly striking and snapping in character. The apex impulse in activated hyperthyroidism tends to be impressively tumultuous and thrusting so that it is diffused over the entire precordia. The apex beat of apathetic hyperthyroidism is not at all of this character. It is not striking. It is not forceful and is not diffused over the precordia. Patients with activated hyperthyroidism tend very distinctly to have a youthful appearance, even those patients of advanced years who show the activation type of hyperthyroidism are made to look much younger than they really are. This is due to the fact that patients with activated hyperthyroidism are energetic, quick in motion, their skin is warm, moist and flushed and of the soft velvety texture which so frequently is associated with youth, while the skin of patients with apathetic hyperthyroidism is quite the opposite and causes their general appearance to be one of greater age than they actually are. Thus, the skin in patients with apathetic hyperthyroidism is cool, dry, wrinkled and pigmented, and in addition the patient is tired, sluggish, and even apathetic. All these features tend to give the patient with apathetic hyperthyroidism an appearance of advanced years as compared with the converse youthfulness of patients with activated hyperthyroidism. Patients with activated, typical exophthalmic goitre usually have had the disease over a shorter period of time than those with apathetic hyperthyroidism. Patients with apathetic hyperthyroidism tend to have the disease in a rela-

tively non-activated form over several months or several years. The weight loss in the activated typical hyperthyroidism is fluctuating, there being periods when there is considerable weight loss and periods in which it is regained. The weight loss in apathetic hyperthyroidism tends to be marked. It occurs quite gradually but progressively over a long period of time, so that it is not an impressive feature in the patient's mind. The basal metabolism of typical activated hyperthyroidism tends to be high, from plus forty, fifty and sixty upwards, to often over plus one hundred. The basal metabolism of apathetic hyperthyroidism tends to be relatively low, from plus forty downward, even as low as plus twenty.

We have had the opportunity several times to observe the course of patients dying from the two different types of hyperthyroidism and their behavior even in this unfortunate situation is entirely different. Patients with activated hyperthyroidism die in a marked state of agitation. They are delirious. They thrash about and are difficult to control. Their pulse rates rise to uncountable heights. Patients with apathetic hyperthyroidism die in quite an opposite manner. If operated upon, they go back to their beds, often with pulse rates of one hundred and twenty or under, in no way agitated, and sink gradually and apathetically into stupor, coma and death.

The course of the two conditions under the stress of an operative procedure is also quite different. Patients with activated hyperthyroidism, while being operated, frequently show marked elevation in pulse rate and marked general activity, while those

with apathetic hyperthyroidism, while being operated upon, frequently show pulse rates ranging between one hundred and one hundred and twenty, not of the toxic character and, in addition, show no signs of activation

These patients with apathetic hyperthyroidism are those in whom unexpected fatalities frequently arise. They are the patients in whom, because of their low basal rate, their lack of pre-operative activation and agitation, their apparent repose, and their apparently safe course while on the operating table or under any stress too much surgery is done at one time. They are the patients in whom we have had practically all of our unexpected fatalities in the surgery of hyperthyroidism. Patients with activated hyperthyroidism are so impressive as to the intensity of their intoxication that the fact that a dangerous condition exists is always uppermost in one's mind. This is distinctly not true of the patients with apathetic hyperthyroidism and one is not infrequently led into a false sense of security, because as a matter of actual experience, it is the patient with apathetic thyroidism,—that is, the patient with marked weight loss, with hyperthyroidism of long standing, the non-activated patient past fifty years,—in whom the addition of any extra burden, operative or non-operative, will result in an unexpected fatality.

We are of the opinion that because of the lack of striking signs and symptoms many of these patients, particularly with small thyroids, go a number of months and years undiagnosed, and we are so distinctly of the opinion that they are particularly bad risks that we have assumed the position that

any patient showing apathetic hyperthyroidism, no matter how good he may appear as a risk, must be operated upon in two stages,—a right subtotal hemithyroidectomy being done first, the patient sent home for six weeks, during which time there is usually marked improvement, to then return to the hospital for a second stage removal of the left lobe.

We have been able to maintain a mortality in the entire series of 9300 thyroid operations of not over one per cent, and within the last few years we have been able to reduce the mortality in toxic goitre to a range of from 0.27 per cent to 0.6 per cent. This includes thyrocardiacs, patients who have been in thyroid crises, and also patients with apathetic hyperthyroidism. It includes the entire group of thyroids coming to the Clinic without rejection. We believe, however, that this mortality rate can be maintained only by an appreciation of the fact that the most serious risks are not in the patients who appear to be in the most serious state, but in those patients of older years, with slow and progressive weight loss, who are apparently good risks, but actually a group in which we have the highest mortality rate.

CONCLUSIONS

A very large percentage of patients who are permitted to get into the advanced state of thyroid crisis will die. Their salvation is the early detection of an impending thyroid crisis or undue intensification of their hyperthyroidism and its emergency treatment with iodine, morphine, amytal, avertin.

salt solution and glucose. By the early application of these measures, patients may be kept out of thyroid crises, prepared and operated by subtotal thyroidectomy within three weeks and definitely relieved of their thyroidism.

Apathetic hyperthyroidism is a state characterized by signs and symptoms quite contrary to those of typical activated hyperthyroidism. It is misleading, not only as to its existence, but it is also misleading as to its seriousness, and possesses graver dangers of a fatality under stress or operative procedure than does the typical activated hyperthyroidism. An appreciation of

its atypical signs and symptoms will result in its early diagnosis and an appreciation of its certain unobtrusive seriousness should make one realize the possibilities of a fatality when the patient is submitted to any considerable extra burden, particularly such as subtotal thyroidectomy in one stage. It should make one undertake surgical procedures in all patients of this type, no matter how good they appear as risks, in two stages. Its earlier recognition and submission to surgery will result in a considerable lowering of its operative and non-operative mortality rate.

Fallacies and Dangers in the Treatment of Exophthalmic Goiter by Iodine*†

By WILLARD OWEN THOMPSON, M D, F A C P, and
PHEBE K THOMPSON, M D, *Chicago, Ill*

UNTIL about ten years ago, the treatment of exophthalmic goiter by iodine was considered a dangerous procedure, although it was not claimed that its immediate effects were always harmful. The attitude then prevalent is fairly well expressed in the statement of T Kocher¹ "Es ist ein zweischneidigen Schwert und der Schaden überwiegt" (it is a two-edged sword and harm predominates). Following the demonstration of the clinical improvement and the reduction in basal metabolism during its administration to patients with toxic goiter², the pendulum swung almost completely to the other extreme. The consequence has been that most beneficial results that occur during its administration are attributed to iodine and most unfortunate results to the natural course of the disease. This is perhaps inevitable and it will probably be several years before the effects of iodine are precisely defined from an unprejudiced point of view. In the meantime, certain considerations appear pertinent.

*Received for publication, September 3, 1931.

†From the Department of Medicine, Rush Medical College and the Presbyterian Hospital, Chicago, Ill.

IODINE AND THE MORTALITY RATE

It is generally agreed that iodine, by reducing the intensity of the disease, has diminished the risk of operation. However, it would seem that the reduction in mortality caused by iodine is often overestimated. Before the days of iodine the mortality had steadily diminished as experience in treating the condition increased. From 1894 to 1907, according to the table in Crotti's³ book, it varied from 2.85 to 30.0 per cent with a mortality over 10 per cent in ten of twenty-three reports. From 1908 to 1917 it varied from 0 to 13.1 per cent (excluding one report in which data were collected from the literature without dates being given) and it was over 5 per cent in only seven of twenty-eight reports. The Mayos⁴ had 4 deaths in their first 16 operations, 3 in the next 30 and 3 in the next 150. From 1907 to 1920 their mortality varied from 2 to 5 per cent, with the general trend downwards and it was, for the most part, under 3 per cent after 1912. For the years 1921, 1922, 1924, 1925, 1926, 1927 and 1928 it was 3.39, 1.74, 0.8, 1.1, 0.83, 0.7, and 1 per cent respectively, according to Pemberton⁵. Iodine

was introduced at the Mayo Clinic in March, 1922

Crile⁶ in 1920 published a chart showing his mortality from June 28, 1906, to October 1, 1919. At first he used ether alone for anesthesia and his death rate was 16 per cent in the first 50 operations. Then with anociation, nitrous oxid-oxygen and local anesthesia with anesthetization of patients in their rooms, the mortality promptly dropped to 4 per cent. It then fluctuated between 2 and 5 per cent for several years until the adoption of his "new technique," which still further reduced the element of fear. With this the rate in exophthalmic goiter was 11 per cent, and in all thyroidectomies it was 0.6 per cent. In 1929 he⁷ reported a mortality of 0.6 per cent in his last 1000 thyroidectomies.

Lahey, in 1916⁸, reported the mortality as varying from 2 to 7 per cent in his operations for exophthalmic goiter. In 1922⁹ this had been reduced to about 1.7 per cent, a rate which was little affected by iodine because this element although introduced into his clinic in 1922, was used only in occasional cases at first. For the five-year period from 1925 to 1929, the mortality as given by Clute¹⁰ was approximately 0.2, 1.8, 1.6, 0.7, and 0.1 per cent respectively.

Porter¹¹, in 1923, reported the results of thyroidectomy in 204 cases of exophthalmic goiter as follows:

1904-1908	No mortality
1909-1914	15 per cent
1914-1919	14 per cent
1919-1920	8 per cent
1920-Jan 1921	3 per cent

Crotti³ gives Kocher's mortality as follows:

Year	No Cases	Death Rate (per cent)
1902	59	6.5
1906	167	5.0
1910	376	4.0
1911	167	2.3
1912	130	1.5
1916	300	1.0

Richter¹², in 1929, reported a mortality of 0.2 per cent in 500 consecutive thyroidectomies, whereas his rate was 1.0 per cent before iodine. In 1920, Frazier¹³ was able to report a mortality for toxic goiter for the preceding five years of between 1 and 2 per cent. Riedl¹⁴ had a mortality of 40 per cent in his first 40 cases and 3.3 per cent in the following 30. Crotti's³ mortality was 8 per cent in his first 100 cases, 7 per cent in the next 122, 3.2 per cent in the next 100, and there were no deaths in the last 137 cases he reported in 1917.

It may thus be seen that in many good clinics before the days of iodine, the mortality from operations for toxic goiter was as low as 1 per cent, and that in the hands of leading surgeons it has dropped from about 1 to 4 per cent to about 0.25 to 0.7 per cent since the introduction of iodine. In spite of iodine, some good surgeons now have a higher mortality than others before the days of iodine. Thus von Eiselsberg¹⁶ reported a mortality of 6 per cent in 1930, and Dunhill¹⁷ of 2.7 per cent in 1930. In fact, Bevan¹⁸ is of the opinion that the average mortality for this country at present is between 3 and 5 per cent. In interpreting such data it must, of course, be borne in mind that a thyroid operation before the days of iodine was usually less extensive than now and that some patients who previously would have died

before operative interference was possible, are now operated upon

REST AND THE IODINE REACTION

In cases of toxic goiter, it is common practice to determine the basal metabolism the day after admission to the hospital and again one or two days before operation, and to attribute any reduction that may have occurred in the interval to iodine. Striking clinical improvement and reduction in basal metabolism often occur from rest alone, whether patients are completely confined to bed or whether they are allowed the usual privileges of ambulatory ward patients. Most of the immediate reduction from rest appears to occur in the first few days.¹⁹ In trying to determine the range of effective iodine dosage in exophthalmic goiter, we²⁰ observed the effect of the daily administration of roughly 0.75 mg., 1.5 mg., 3.0 mg., and 6 mg. of iodine. It so happened that in the case of the two smallest doses, the effect of rest was greater than the effect of the small doses of iodine and, in the case of the second largest dose, its effect was just as great. It would, therefore, have been impossible to compare the effects of these different doses of iodine without having secured a level of basal metabolism during rest. Similarly the amount of clinical improvement and the amount of reduction in basal metabolism caused by large doses of iodine in any part of the country can be accurately gauged only when the effect of rest alone on these two factors under the same conditions is determined.

REFRACTORINESS TO IODINE AND ITS MANAGEMENT

It is important to determine whether patients with exophthalmic goiter ever develop a tolerance to iodine. Many observers have reported that, during its prolonged administration, the basal metabolism, after showing an initial reduction, may rise to a higher level than it was before iodine was started, and the patient becomes worse. In spite of this, it has been claimed that the peculiar nervous manifestations of the disease are always under control at all stages in this response and that the variations in metabolism are the result of spontaneous variations in the disease and independent of the iodine. Thus, according to this theory, iodine should never be omitted because its effect never wears off while it is being given in excess.

Our experience has not led us to a similar conclusion. In patients whom we have observed when the metabolism was rising in spite of the administration of iodine, all of the manifestations of the disease including the peculiar nervous ones, were becoming more marked. Under such circumstances, we have seen exophthalmos not only increase but appear for the first time.²¹ The end result of such a reaction may be the development of refractoriness to iodine, examples of which have been reported elsewhere.²¹ When patients are refractory the disease usually flourishes in a severe form. We²¹ have elsewhere reported a patient who had a thyroidectomy when his metabolism was rising rapidly during the administration of iodine and who died of a typical crisis sixty hours after opera-

tion There had been a marked temporary improvement which had lasted only a short time before the metabolism began to rise Before the days of iodine, many observers (e. g., Means²², Mayo²³, Crotti³, Plummer²⁴, Else and Irvine²⁵) had pointed out that it was unsafe to operate during a period of rising metabolism This would still appear to be a contraindication to operation, even if iodine is being administered

That patients may become refractory to iodine during its prolonged administration is supported by the observation of several workers Jackson²⁶ has noted that "the greatest risks (i. e., operative) occur when patients have been given iodine for many months until they develop a tolerance to it", in such patients "the same reaction" after operation "is expected as before iodine was used" According to Graham²⁷, "clinical experience has demonstrated the utter futility of further iodine therapy in the already overiodinized patient" He considers such patients poor operative risks. Frazier and Mosser²⁸ have gone so far as to say that indiscriminate and prolonged administration of iodine "has to a large extent deprived the surgeon of this safeguard, and we have again been forced to operate in an increased number of cases by the fractional method" Graham²⁹, Campbell³⁰, and Goetsch³¹ are of the impression that operation in a patient who shows a high metabolism and is very sick after the prolonged administration of iodine may cause the death of the individual.

The possibility must, therefore, be considered that in certain cases of exophthalmic goiter the administration of

iodine may stimulate some reaction to it which tends to counteract its beneficial effect In support of this is the fact that a dose of iodine which in itself is too small to cause any reduction in basal metabolism, may interfere with the effect of much larger doses administered immediately afterward³².

The percentage of patients that will develop refractoriness to iodine during its prolonged administration is unknown Refractoriness appears to us to occur primarily in moderately severe and severe cases rather than in mild cases³³ We have reported mild cases in which the metabolism could be held depressed at a constant level for years by continuous administration of iodine^{33,34} The importance of operating as soon as the maximum reduction in basal metabolism occurs seems to us to have been exaggerated It appears safe to postpone operation at least from one to two weeks beyond the time of maximum reduction in all but the more severe cases In other words, it would seem that the more severe the case the more rapidly refractoriness develops

Contrary to the general belief, it has been our experience that after a short period of freedom from iodine (usually four weeks) patients will lose their refractoriness to it and again show a well marked response Both Graham²⁷ and Coller³⁵ have observed a similar phenomenon Thus, in all patients who have developed marked refractoriness to iodine, it seems to us unwise to resort to any operative interference until iodine has been omitted long enough for the refractoriness to disappear^{21, 36}

It should be emphasized that iodine

has not completely abolished postoperative reactions. It has merely reduced their number and intensity. We still occasionally see severe reactions in patients who show a well marked improvement during the preoperative administration of iodine. One of our patients recently died from a typical crisis 60 hours after operation, in spite of the fact that her basal metabolism had dropped from plus 100 to plus 30 per cent and her pulse from 120 to 60 with rest and iodine before operation. Most clinics still report a few deaths each year from postoperative crises in spite of iodine administration, although, of course, the number has been markedly reduced (e g., at the Mayo Clinic from 1 per cent to 0.14 per cent³⁷).

Lahey³⁸ has remarked "It is distinctly possible that the apparent improvement following the use of Lugol's may be so great that one is led to do a complete operation only to have the patient die in intense thyroidism." Clute³⁰ of the same Clinic has said "With multiple stage operations the mortality of primary hyperthyroidism was reduced to less than 1 per cent in this clinic and we hesitated to adopt the more radical procedure of thyroidectomy in one stage, which was popular after iodine preparation. In 1925, however, we became more radical and, to a large extent, we permitted iodine to replace pole ligations. The number of stage operations fell from 65 per cent, the figure before iodine was used, to 21 per cent. The mortality rose at once to 2.06 per cent." Dunhill¹⁷ has very aptly remarked that iodine "has helped so greatly that the literature would lead us to believe that the opera-

tion is now quite safe, that the necessity for ligations of arteries has passed and that generally the complete procedure may be employed in one stage. To some extent this is true but it is not completely true." It is his impression that unless graded operations are carried out in patients who do not respond well to iodine "the death rate will be unduly high."

Observation of a large number of patients at all stages in their response to iodine has convinced us that iodine does not cause the complete disappearance of the emotional manifestations of the disease, it merely reduces their intensity, which varies roughly with the basal metabolism. It sometimes may exert no apparent influence. Lahey³⁰ and Clute⁴⁰ have reported patients who died in crisis before operation could be considered, in spite of "the most active measures including iodine in large doses." Increasing experience with iodine thus seems to justify the conclusion that the control it exercises over the disease is relative and not absolute, and that after it has been administered for a long time, its beneficial effects may disappear entirely. In other words, there is more to the treatment of exophthalmic goiter than the administration of iodine and the performance of a subtotal thyroidectomy. The lessons learned before the days of iodine cannot be ignored now if the mortality is to be kept at a low level. Among factors that seem to be of importance in achieving this end may be mentioned

- 1 The skill of the surgeon
- 2 Proper selection of the time of operation—in particular avoiding operative interference at times when the

patient has developed or is developing refractoriness to iodine

3 The type of operation.

4 A diet sufficiently high in calories to make the patient gain weight before operation. This should also be high in protein (roughly 1.5 to 2 grams per kilogram of body weight), because of the rapid breakdown of protein in this disease.

5 Abolition of fear, worry and other psychic traumata.

6 Attention to fluids and calories in the immediate postoperative period.

7 Proper selection of an anesthetic.

About the third point there is some dispute. Before the days of iodine, most surgeons were of the impression that stage operations had been a factor in reducing the mortality. Several observers, notably those at the Lahey Clinic¹⁰, still insist that they should be done in all doubtful cases and consider them important in their low mortality. Richter¹², on the other hand, has always maintained that his low mortality, even before iodine, has in part been the result of rarely doing a thyroidectomy in more than one stage. Richter's mortality is about the same as Lahey's. We are somewhat at a loss to reconcile these divergent points of view.

We wish to make it clear that this is not an attempt to minimize the value of iodine in the treatment of exophthalmic goiter. Indeed, we regard the treatment of this disease with iodine as one of the most important advances in recent times. We do feel, however, that accurate evaluation of the effects of iodine will save us from certain pit-

falls of the past and will in no way detract from its importance.

SUMMARY

Since the introduction of iodine the mortality from thyroidectomy for exophthalmic goiter in the leading clinics, has been lowered from about 1 to 4 per cent, to about 0.25 to 0.7 per cent. This reduction is, we believe, less than is generally appreciated.

The actual clinical improvement and reduction in basal metabolism caused by iodine is also somewhat less than is generally appreciated, owing to the fact that the influence of rest is usually not controlled.

In very severe cases of the disease operation should be performed as soon as the metabolism reaches a level during the administration of iodine, because the beneficial effects in such cases may be of short duration.

In cases in which the basal metabolism is high after the prolonged administration of iodine and those in which the basal metabolism is rising rapidly during the administration of iodine, no operative procedures should be undertaken until iodine has been omitted long enough for the refractoriness to it to disappear (usually about four weeks), and then readministered.

In the routine preoperative treatment of exophthalmic goiter it is desirable to give suddenly an adequate excess of iodine and not to precede this with small doses.

A few patients still die from typical postoperative thyroid crises in spite of the administration of large doses of iodine. These reactions sometimes occur in patients who have shown satisfactory responses to iodine before operation.

There is more to the treatment of exophthalmic goiter than the administration of iodine and the performance of a subtotal thyroidectomy. The skill of the surgeon, selection of the time and type of operation, proper attention

to calories, protein, and fluid in the preoperative and postoperative periods, abolition of fear and worry, and the type of anesthesia, all seem to be factors of importance in keeping the mortality low.

REFERENCES

- ¹KOCHER, T. Über Jodbasedow, Verhandl d deutsch Gesellsch f Chr, 1910, xxxix, 396
- ²PLUMMER, H S. Results of administering iodine to patients having exophthalmic goiter, Jr Am Med Assoc, (Soc Proceedings), 1923, lxxx, 1955
- PLUMMER, H S, and BOOTHBY, W M. The value of iodine in exophthalmic goiter, Jr Iowa Med Soc, 1924, xiv, 66-73
- NEISSER, E. Über Jodbehandlung bei Thyreotoxikose, Berl klin Wchnschr, 1920, lvi, 461-463
- LOEWY, A, and ZONDEK, H. Morbus Basedowii und Jodtherapie, Deutsch med Wchnschr, 1921, xlvii, 1387-1389
- ³CROTTI, A. Thyroid and thymus, 1918, Lea and Febiger, Philadelphia and New York, p 411
- ⁴MAYO, C H. Mortality and late results from thyroidectomy in exophthalmic goiter or hyperthyroidism, Trans Am Surg Assoc, 1908, xxvi, 597-598
- A consideration of the mortality in one thousand operations for goiter, Surg Gynec and Obst, 1909, viii, 237-240
- The operative treatment of hyperthyroidism, Surg Gynec and Obst, 1907, viii, 602-605
- A consideration of surgical methods of treating hyperthyroidism, Med Rec, 1910, lxxviii, 1173-1174
- Observations on the thyroid gland and its diseases, Surg Gynec and Obst, 1912, xiv, 363-368
- Factors of safety in operating for exophthalmic goiter, Jr Am Med Assoc, 1912, lix, 26-27
- Surgery of the thyroid—observations on five thousand operations, Jr Am Med Assoc, 1913, lxi, 10-13
- MAYO, C H, and PLUMMER, H S. Goiter and life expectancy, Lancet-Clinic, 1915, cxiii, 649-651
- BERKMAN, D M. Preoperative considerations of exophthalmic goiter, St Paul Med Jr, 1916, xviii, 300-303
- PEMBERTON, J deJ. Goiter, management of the poor surgical risk, Arch Surg, 1930, xx, 591-606
- ⁵PEMBERTON, J deJ. The surgical management of toxic goiters, Bost Med and Surg Jr, 1922, clxxxvi, 244-254
- The end-results of surgery of the thyroid gland, Arch Surg, 1923, vii, 37-46
- PEMBERTON, J deJ. Present-day surgical treatment of diseases of the thyroid gland, Jr Am Med Assoc, 1925, lxxxv, 1882-1886
- Modern management of exophthalmic goiter, Calif and West Med, 1926, xxi, 619-622
- Causal factors in the surgical mortality rate of exophthalmic goiter, NY State Jr Med, 1928, xxviii, 256-261
- Exophthalmic goiter indications for the stage-operation, Arch Surg, 1929, lviii, 735-744
- Goiter management of the poor surgical risk, Arch Surg, 1930, xxi, 591-606
- ⁶CRILE, G W. The surgical treatment of exophthalmic goiter, Surg Gynec and Obst, 1920, xxx, 27
- ⁷CRILE, G W. The adrenal factor in hyperthyroidism, Surg Gynec and Obst, 1929, lviii, 371-374
- ⁸LAHEY, F H. Partial thyroidectomy with local anesthesia, scopolamine and morphine, Bost Med and Surg Jr, 1916, clxxv, 566-568
- ⁹LAHEY, F H. A review of a year's thyroid work, Bost Med and Surg Jr, 1922, clxxxvi, 563-568

- ¹⁰CLUTE, H M. The operative mortality in hyperthyroidism, *Jr Am Med Assoc*, 1930, xci, 389-392.
- ¹¹PORTER, C A. Analysis of my end-results in thyroid surgery, *Surg Gynec and Obst*, 1923, xxxvi, 621-640
- ¹²RICHTER, H M. Thyroidectomy, *Surg Gynec and Obst*, 1929, xlix, 67-75
- ¹³FRAZIER, C H. The management of toxic goiter from the surgical point of view, *Ann Surg*, 1920, lxxii, 155-160
- ¹⁴RIMM, quoted by CROTTI, see reference 3
- ¹⁵VON EISENBERG, A. *Handbuch der praktischen Chirurgie*, 1927, E Enke, Stuttgart
- ¹⁶DUNNILL, T P. Toxic goitre, *Brit Jr Surg*, 1930, xvii, 424-450
- ¹⁷BLAIR, A D. Personal communication
- ¹⁸THOMPSON, W O, BRAILEY, A G, THOMPSON, P K, and THORP, E G. The range of effective iodine dosage in exophthalmic goiter I The effect on basal metabolism of rest and of the daily administration of one drop of compound solution of iodine, *Arch Int Med*, 1930, xlv, 261-281
- THOMPSON, W O, THORP, E G, THOMPSON, P K, and COHEN, A C. The range of effective iodine dosage in exophthalmic goiter II The effect on basal metabolism of the daily administration of one-half drop of compound solution of iodine, *Arch Int Med*, 1930, xlv, 420-429
- THOMPSON, W O, COHEN, A C, THOMPSON, P K, THORP, E G, and BRAILEY, A G. The range of effective iodine dosage in exophthalmic goiter III The effect on basal metabolism of the daily administration of one-quarter drop of compound solution of iodine and slightly smaller doses, with a summary of results to date, *Arch Int Med*, 1930, xlv, 430-455
- THOMPSON, W O, THOMPSON, P K, and COHEN, A C. The range of effective iodine dosage in exophthalmic goiter IV The effect on basal metabolism of the daily administration of about 0.75 mgm of iodine, *Arch Int Med*, 1932, xlix, 199-214
- STURGIS, C C. Observations of one hundred and ninety-two consecutive days of basal metabolism, food intake, pulse rate and body weight in a patient with exophthalmic goiter, *Arch Int Med*, 1923, xxxii, 50-73
- MEANS, J H, and ALLEN, J C. A study of exophthalmic goiter from the point of view of the basal metabolism with remarks concerning the effect of various forms of treatment, *Jr Am Med Assoc*, 1917, lxix, 33-37.
- KISSEL, L, LEEB, C C, and HAYMAN, H T. A study of exophthalmic goiter and the involuntary nervous system, IX. An estimation of the pathogenesis and the evaluation of therapeutic procedures in exophthalmic goiter, *Jr Am Med Assoc*, 1922, lxxix, 1213-1216
- ¹⁹See reference 19. First four references
- ²¹THOMPSON, W O, and THOMPSON, P K. Exophthalmic goiter, the development of refractoriness to iodine, *Arch Int Med*, 1931, xliiii, 351-376
- ²²MALORY, T B; MEANS, J H and YOUNG, E L JR. Exophthalmic goiter and acute rheumatic fever, Case No 15472, *New England Jr Med*, 1929, cci, 1056
- ²³MAYO, C H. Observations on the thyroid gland and its diseases, *Surg Gynec and Obst*, 1912, xiv, 363-368
- ²⁴PLUMMER, H S. The clinical and pathological relationship of simple and exophthalmic goiter, *Am Jr Med Sci*, 1913, cxlvi, 790-795
- ²⁵ELSER, J E, and IRVING, H S. The causes of surgical failure in hyperthyroidism, *Jr Am Med Assoc*, 1922, lxxix, 1289-1291
- ²⁶JACKSON, A S. Diseases of the thyroid gland, *Wis Med Jr*, 1930, xxix, 327-332
- ²⁷GRAHAM, A. Preoperative iodine therapy in toxic goiter indications and limitations, *Am Jr Surg*, 1927, ii, 354-358
- ²⁸FRAZIER, C H, and MOSSER, W B. End-results from the surgical treatment of hyperthyroidism, *Jr Am Med Assoc*, 1928, xc, 657-659
- ²⁹GRAHAM, D. Personal communication
- ³⁰CAMPBELL, W W. Personal communication
- ³¹GOETSCH, E. The use and misuse of iodine in the treatment of toxic goiter,

NY State Jr Med, 1927, xxvii, 1075-1080

³²Reference 19 Third and fourth references

³³THOMPSON, W O, THOMPSON, P K, BRAILEY, A G, and COHEN, A C Prolonged treatment of exophthalmic goiter by iodine alone, Arch Int Med, 1930, xlv, 481-502

³⁴THOMPSON, W O, MORRIS, A E, and THOMPSON, P K Thyrotoxicosis following subtotal thyroidectomy for exophthalmic goiter, Arch Int Med, 1930, xlv, 946-978

³⁵COLLER, F A The use of iodine in the treatment of goiter, Ann Clin Med, 1926, v, 91-94

³⁶JACKSON, A S The use of iodine in hyperthyroidism, Am Jr Surg, 1929, vi, 7-10 (Jackson states that he has

been able to produce improvement in some of these patients by administering enormous doses of iodine Experience we have had in determining the range of effective iodine dosage in exophthalmic goiter does not seem to support his contention)

³⁷PEMBERTON, J deJ Goiter, management of the poor surgical risk, Arch Surg, 1930, xx, 591-606

³⁸LAHEY, F H The use of iodine in goiter, Bost Med and Surg Jr, 1925, cxciii, 487-490

³⁹LAHEY, F H The management of goiter, Jr Ind State Med Assoc, 1930, xxiii, 117-122

⁴⁰CLUTE, H M Effect of compound solution of iodine and rest in surgery of exophthalmic goiter, Jr Am Med Assoc, 1926, lxxxvi, 105-109

Subacute Bacterial Endocarditis Following the Extraction of Teeth: Report of a Case*†

By MITCHELL BERNSTEIN, M D , F A.C P , *Philadelphia, Pa*

SUBACUTE bacterial endocarditis may be overlooked, or it may be masked as another disease, as in the case to be reported, for some weeks, before the true nature of the disease is recognized. Moreover, the importance of being mindful of this disease in every case of illness associated with continued fever, cannot be over emphasized.

Jules B, aged 25, a law student, complained on January 15, 1931, of having a slight fever every afternoon, night sweats of moderate severity and weakness.

His family history was essentially negative. During childhood he had measles, mumps, diphtheria and chorea. In addition, he had rheumatic fever when he was eight years of age. Subsequent to this he was told that he had "some valvular lesion" although it apparently caused him no discomfort or incapacity.

The present illness dated from December 20, 1930, when two non-vital abscessed molar teeth were extracted under local anesthesia. Following the extraction of these teeth, the patient bled profusely. Packing of the teeth sockets was necessary and despite this procedure the bleeding continued for three days. On the fifth day following the extraction of the teeth, the patient developed fever but had no other definite symptoms. The fever continued and on January 5, 1931,

the patient consulted a physician who advised return for dental examination. The teeth sockets were curetted and free drainage instituted. Despite this procedure the fever continued, ranging from 99°F to 100°F. Meanwhile the patient was up and about, attending to his daily routine. He consulted several physicians who told him that he had a mild attack of grippe.

On January 15, 1931, 26 days after the extraction of the teeth the patient first came under my observation. His temperature was 102°F. He was rather pale. The site of the dental extraction showed no signs of infection. The tonsils were absent. There was a pulsation at the root of the neck. Physical examination of the lungs showed no abnormalities.

The heart was enlarged to the left, the apex being in the fifth left interspace, 14 cm to the left of the midsternal line. The right border of the heart was at its normal position. No thrill was palpable. On auscultation at the apex of the heart, a soft systolic murmur was heard and this was transmitted to the left axilla. In addition, at the aortic area, an aortic diastolic murmur was heard and this was transmitted down the left side of the sternum. The heart rate was 100 to 110 per minute and the blood pressure was 120 systolic, and 60 diastolic. A Corrigan's pulse was present.

The examination of the abdomen was essentially negative except for a slight enlargement of the spleen on percussion. Examination of the extremities was negative. The urine proved to be normal. The blood count showed 13,800 leucocytes of which 86 per cent were polymorphonuclears.

On January 16 the blood count showed 13,000 leucocytes of which 90 per cent were

*From the service of Dr Thomas McCrae, Jefferson Medical College Hospital, Philadelphia, Pa

†Submitted for publication, July 1, 1931

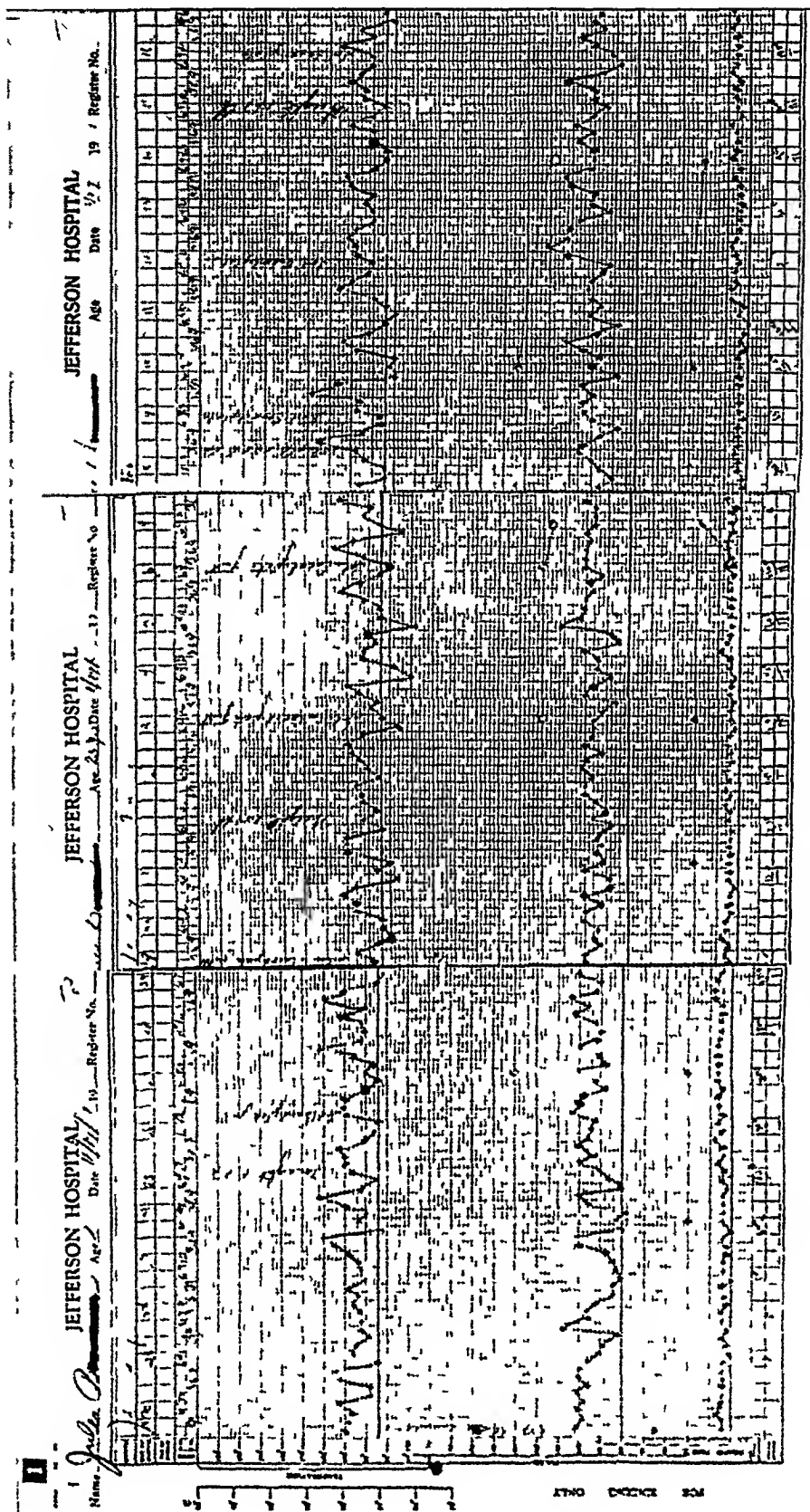


CHART 1 A The temperature and pulse ranges throughout the course of the disease

2

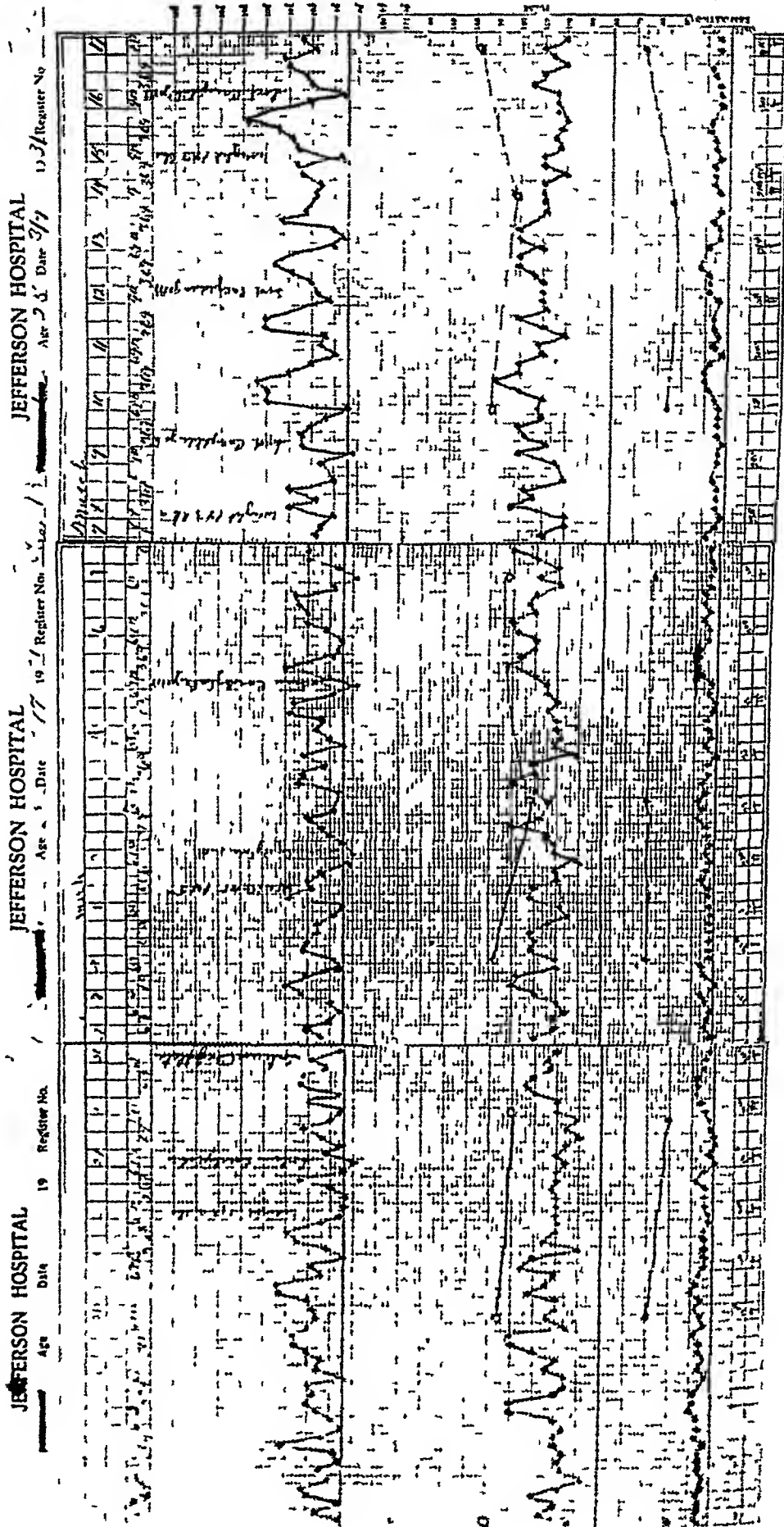


CHART 1B The temperature and pulse ranges throughout the course of the disease

polymorphonuclears, while on January 17 the blood count showed 12,000 leucocytes and 85 per cent polymorphonuclears

In view of the history of previous rheumatic fever together with clinical evidence of valvular disease, involving the aortic and mitral valves, the diagnosis of subacute bacterial endocarditis was made

A blood culture which was taken in the meantime, showed after 48 hours, a profuse growth of *streptococcus viridans*

On January 19, 1931, the patient was admitted to the service of Dr Thomas McCrae, at the Jefferson Medical College Hospital. The blood count showed 87 per cent hemoglobin, 4,410,000 red blood cells, 12,300 leucocytes, 86 per cent polymorphonuclears, 13 small mononuclears and 1 large mononuclear. A blood culture taken following the patient's admission to the hospital, showed a profuse growth of the *streptococcus viridans*. Subsequent cultures of the patient's blood taken at intervals, always showed the *streptococcus viridans*.

The fever continued, as did the night sweats. The physical signs remained practically unchanged until March 1, 1931. At that time there was tenderness over the spleen. The tips of the patient's fingers were tender and showed a few small embolic areas.

On March 16, 1931, the patient complained of blurred vision. Additional embolic areas were present in the finger tips on March 30. There was considerable precordial distress and palpitation.

On April 19, the patient complained of severe pain in the region of the spleen. This organ was tender and on percussion was found to be enlarged. The pain in the splenic area continued for three days. Pain over the spleen recurred on April 27 and a friction rub was detected over the splenic area. Meanwhile the fever was continuous, the temperature ranging from 97°F to 102°F and later reaching 104°F, as will be seen from the temperature chart (temperature chart reproduced). The anemia was slightly increased. Blood cultures continued to be positive for the *streptococcus viridans*. The patient had become quite emotional and very apprehensive.

On May 18, the physical signs of congest-

tion were detected in the left lung, at the base, posteriorly. In addition, the heart rate was 120 to 130 per minute. On auscultation the aortic diastolic murmur was very loud as was the mitral systolic murmur.

The following morning, May 19, at 2 10 A M., the patient died.

The duration of the illness from the time of the onset of symptoms was about six months.

Post mortem examination was not permitted.

Additional Data. Daily examination of the urine failed to show red blood cells at any time during the course of the disease. The specific gravity varied from 1004 to 1022. There was from a faint trace to a trace of albumin, and at times none. Casts were found in the urine toward the termination of the disease. Blood cultures were taken on January 22, 27, February 4, 25, March 4, and April 8 and proved positive for *streptococcus viridans*.

Various blood counts done at intervals were as follows:

		Hg	RBC	WBC	Poly	SM	I M	Eosin
Jan 20	87%	4 410,000	12 300	86	12	2	2	
Jan 30	78%	4 100,000	12,000	70	24	4	2	
Feb 12	76%	3 050,000	13 000					
Feb 24	72%	4 030,000						
Mar 31	82%	4 200 000	14 000	65	25	8	2	
May 1	76%	3,900,000	19,000	72	24	2	2	
May 11	75%	4,020,000	15,600					

On February 11, 1931, the icterus index was eight units. The Van den Bergh test showed an indirectly weakly positive reaction. The blood Wassermann reaction was negative.

Various forms of treatment were used but all proved of no avail.

COMMENT

The occurrence of the infection within five days following the extraction of the teeth and subsequent packing of the sockets raises the question as to whether the infection was disseminated on account of the trauma at the time of the extraction of the teeth or at the time of packing or whether an infection was introduced at the time

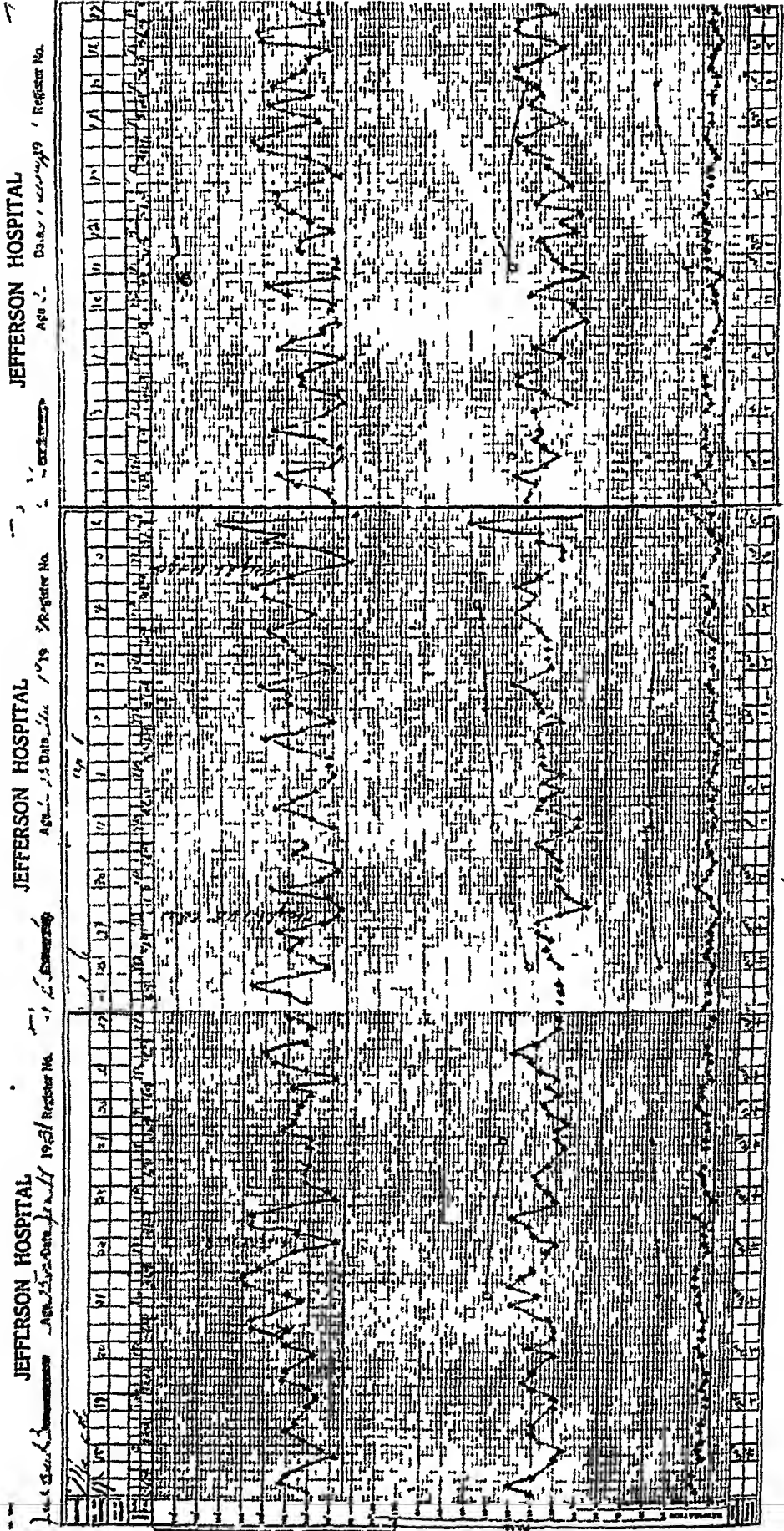


CHART 1C The temperature and pulse ranges throughout the course of the disease

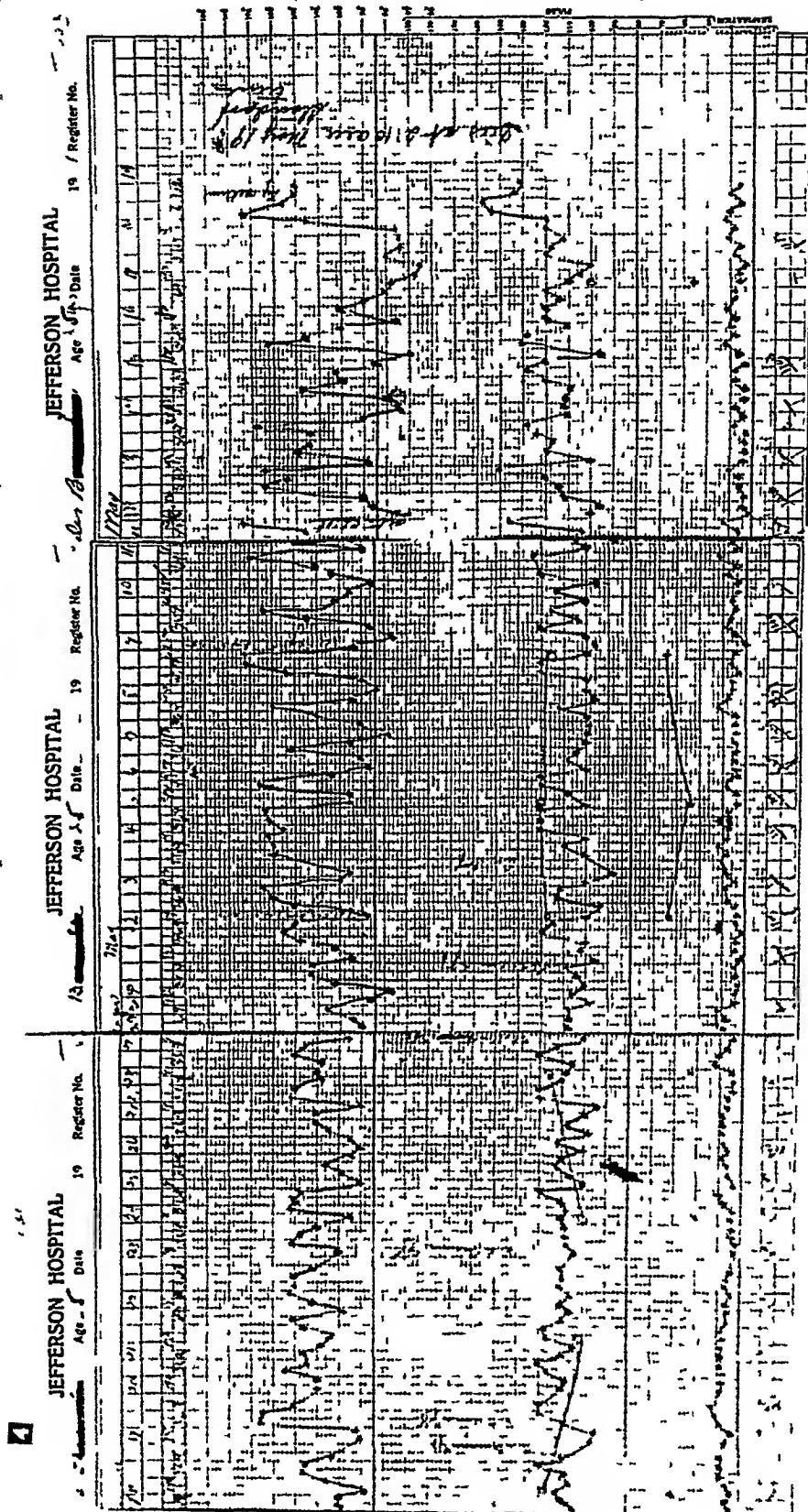


Chart 1D The temperature and pulse ranges throughout the course of the disease

of packing, by the use of materials and instruments which may not have been sterile. At any rate, both procedures should always require absolute sterility of all instruments used by the dental surgeon.

Furthermore, the question of the advisability of removing infected teeth from a patient with rheumatic heart disease, because of the danger of the

occurrence of subacute bacterial endocarditis, seems very pertinent. Although it is a known fact that scores of infected teeth are extracted daily, yet it would seem from the foregoing case report, that the procedure is not without danger. Just how this danger may be avoided by other than the usual precautions of sterility during extraction of teeth, remains a question.

The Management of Coronary Thrombosis and Its Complications*

By BLANTON P SEWARD, A B , M D , F A C P , *Roanoke, Va*

THE increasing frequency with which the diagnosis of coronary thrombosis with myocardial infarction is being made indicates that it is a relatively common disease. In the majority of cases it can be diagnosed at the bedside, but an important aid in its recognition is the electrocardiogram, since clinical and experimental investigations have shown that certain changes in the ventricular complex are associated with obstruction in a coronary artery. While these changes are a valuable aid in the diagnosis, especially of suspicious and atypical cases, they are not invariably diagnostic for they are found in electrocardiograms in other cardiac conditions. Electrocardiography has justifiably achieved a place of importance in the diagnosis of coronary thrombosis, and recent work¹ in the correlation of the electrocardiographic phenomena with the pathological changes found in the hearts of patients who have died of coronary thrombosis, indicates the possibility of localizing the region of the coronary system involved by the obstruction with the accuracy that obstructive lesions in the cerebral arteries are localized.

While our knowledge of the clinical features and of the pathological changes subsequent to the thrombosis of a coronary artery has been greatly extended, no fixed methods of treatment of this condition and its complications have been formulated. Methods of treatment found in the literature are no more than brief outlines omitting many details of importance. This is not surprising since it has been only in recent years that the first diagnosis of coronary thrombosis was made. In addition, the rapidity of the progress of the disease in many patients and the suddenness with which complications may arise, make it extremely difficult to evolve a system of treatment. However, bearing in mind the gross anatomical changes which occur in the heart following thrombosis and the pathological physiology accompanying these changes, further experience will aid in working out a more satisfactory plan of treatment. In the light of our present knowledge there are certain principles which may be followed in the proper management of this condition and its complications.

MANAGEMENT DURING THE ACUTE ATTACK

With the onset of the attack the outstanding symptom is pain which

From the Department of Medicine
- Gale Hospital, Roanoke, Va
Submitted for publication, June 1 1931

if possible, should be relieved. The pain may be severe from the first or it may begin as a mild discomfort and increase in intensity until it becomes agonizing. In either instance morphine in sufficient doses, one-fourth to one-half a grain, must be given as often as necessary to control the pain. Coronary thrombosis is one condition in which we are justified in giving large doses of morphine, since it not only gives relief from the pain, but aids in producing mental and physical rest. There is no contra-indication to its use, although when the pain is located in the epigastrium the physician should be reasonably sure before giving much of it that the pain is caused by the occlusion of a coronary artery and not by an acute lesion in the upper abdomen which may require surgical intervention. The continued use of morphine may be necessary for a few days, after which the milder sedatives, such as the bromides and occasional doses of codeine or morphine, will usually allay the pain and restlessness.

The hypnotics and anodyne preparations synthesized from barbituric acid, such as allonal, amytal and luminal, are frequently given to relieve mild pain and restlessness in many conditions, but we prefer not to use them in this disease on account of their depressing effect. The nitrites, so valuable in the treatment of angina pectoris, do not relieve the pain caused by the occlusion of a coronary artery. They are not only useless in this condition, but as a falling blood pressure accompanies thrombosis, these drugs may do harm by reducing the pressure still further.

Soon after the beginning of an at-

tack, a state of shock develops and it should be treated in much the same manner as in other conditions. The body should be kept warm by the application of warm blankets and hot water bottles, but stimulation should be avoided unless heart failure is threatening. In all cases the heart sounds soon become distant, the quality of the first sound indicates poor muscle tone; the regular rhythm may be interrupted by an occasional extrasystole; the systolic pressure may fall to 100 mm of mercury or lower, and an ashen color will be observed. Shock may be of mild degree, and the relief of pain and the application of heat may be all the measures required in the immediate treatment of many of these patients, who will often show improvement in a few days.

Other patients are more severely shocked, especially when the pain persists any length of time. In these the cardiac sounds are more feeble and arrhythmic, the pulse is small in volume or imperceptible, the respirations are irregular and shallow and cyanosis is more pronounced. When such signs prevail gentle stimulation with caffeine sodium benzoate is necessary, in addition to the application of heat and the administration of morphine. Three to five grains of caffeine may be administered intramuscularly every two hours for a few doses or regularly for a day or two according to the requirements of the patient. In small doses caffeine strengthens the heart beat, stimulates the vasomotor center causing vasoconstriction, and stimulates the respiratory center, causing an increase in alveolar ventilation. On the other hand, large doses of caffeine have been

shown experimentally to increase the tendency to cardiac failure by depressing the heart muscles, and also to paralyze the blood vessel walls² Large doses of this drug should not be given Caffeine has a definite place in the treatment of coronary thrombosis and its judicious use appears to carry some of the patients through the crisis If the condition of the patient requires stronger stimulation, eight to ten minims of epinephrine may be given, but in our experience when strong stimulants are required the patient is beyond hope of recovery

There is little that can be done for the nausea and vomiting which are so often present In many patients the nausea subsides in two or three days, while in others it may persist for a week or longer, making it difficult for them to take an adequate amount of nourishment, or of fluid to prevent dehydration When fluid and nourishment cannot be taken by mouth in sufficient amounts, they should be given daily by other routes It is better to avoid giving large amounts of fluid intravenously as the greatly increased volume in the circulation will increase the work of the heart and may still further embarrass its action On the other hand, small quantities of a concentrated solution of glucose may be given intravenously without endangering the heart To patients who have much nausea we give routinely 30 to 40 c c of 50 per cent solution of glucose intravenously once in twenty-four hours, supplemented by 500 to 1000 c c of normal saline with 5 per cent glucose by rectum until they are able to take a sufficient quantity of fluid and food by mouth An improvement

in the quality of the sounds as well as in the volume of the pulse is a common observation after glucose is given intravenously The administration of glucose is physiological in principle and a valuable supporting measure in the treatment of coronary thrombosis since it serves as a source of readily available energy, thus aiding the heart in maintaining its functional integrity The use of glucose should be continued until the patient can take a sufficient quantity of food and fluid by mouth When nausea is very annoying we do not attempt to give anything by mouth for twenty-four to twenty-eight hours except enough water to prevent excessive dryness of the mouth and throat While this does not cause the nausea to subside entirely, in some instances it increases the patient's comfort and enables him to take water and nourishment more easily when oral feeding is resumed

An increase in the blood urea is observed during the first week after coronary thrombosis This increase, due to stasis of the circulation and passive congestion of the kidneys, is usually not marked, although if the patient has chronic nephritis, it may rise to a high figure, as, for example, to 180 mg per 100 c c of blood in a patient seen recently Uremia may then seem imminent, but we have not seen it develop in such patients We do not attempt to reduce the urea since the patient's weakness will not permit the institution of vigorous sweating and purging or the withdrawal of blood followed by the intravenous administration of saline solution, indeed nothing can be done except to give a reasonably large quantity of fluid to increase the urin-

ary secretion, for within two weeks the urea usually returns to its original level. In the patient referred to it decreased to 46 mg in two weeks and remained at that figure.

A complication of coronary thrombosis which we have not seen mentioned in the literature, is cerebral thrombosis. It probably seldom occurs but since all of the patients have cardiac weakness, a low blood pressure, slowing of the rate of the circulation, and many of them have advanced arteriosclerosis—factors which underlie thrombus formation in cerebral arteries—we wonder why cerebral thrombosis does not occur often, especially in those patients who are slow in recovering from the acute attack. The symptoms arising in the course of the following case suggest thrombosis of a cerebral artery eleven days after the occlusion of a coronary artery occurred.

Case Abstract H. C., white male, 66 years of age, was admitted to the Lewis-Gale Hospital on December 15, 1930, complaining of substernal pain and a choking sensation. The pain began suddenly in the epigastrium four days previously, it increased in severity and it was not readily relieved by morphine. After the first day the pain was located chiefly under the sternum. When the patient was admitted to the hospital the pain was severe and it was accompanied by nausea and vomiting. All of the symptoms and signs, including a blood pressure reading of 96/68, indicated coronary thrombosis. The R-T segment of the electrocardiogram showed the modifications associated with thrombosis. According to the work of Barnes and Whitten¹ these changes were classified as of Type T₃, which would indicate that the infarction was in the posterior portion of the left ventricle in the region supplied by the right coronary artery in the average heart.

The pain recurred each day and morphine was given when required. As the persistence

of nausea and vomiting precluded the taking of fluid and solid food, 30 c.c. of 50 per cent solution of glucose was given by vein and 500 c.c. of saline and 5 per cent glucose by rectum daily. By the sixth day a slight improvement was noted in the quality of the heart sounds, the systolic blood pressure varied between 100 and 110 mm., his general condition was better, and the nausea was subsiding.

On December 20, one week after admission, he did not respond to questions, whereas before he had responded readily, his mind was not clear, although he was not unconscious, as he gave evidence of understanding questions and made an effort to talk, there was some difficulty in deglutition, motion and sensation in the right arm and hand, and to a less extent in the right leg, were diminished. Five days later the patient showed some improvement, his mind was more alert, his speech was fairly distinct, and he could move the arm and leg more easily. He died suddenly, probably from cardiac dilatation, on December 25. An autopsy was not permitted.

The mental haziness, the motor aphasia, the diminished sensory perception and motion in both right extremities indicated some disturbance in the circulation of blood in that part of the left frontal cerebral convolution with which the functions of speech and of motion in the right side of the body are associated. Since all the underlying factors of cerebral thrombosis mentioned above were present, and as improvement in these symptoms was observed in five days, we think there was a partial occlusion of a cerebral artery by a thrombus. It is quite possible that these symptoms were due to an embolus instead of the formation of a thrombus in the cerebral artery. The area of infarction in the myocardium may have extended to the endocardium, causing an inflammatory reaction with the formation of a thrombus, which may have been dislodged and carried by the blood to the brain.

If such a complication should occur, little if anything can be done about it, the clinician should continue to direct his attention chiefly to the heart and to the comfort of the patient. In the

case mentioned above we continued the same treatment the patient had been getting before the development of the cerebral symptoms

As in all other cardiac conditions, the possible use of digitalis must be considered in the treatment of coronary thrombosis. In this condition there is a slowing of the rate of the circulation with congestion in the lungs and in the general circulation, although edema rarely occurs. When the measures outlined above for relieving the pain, combating shock, supplying nourishment and gentle stimulation if required, are employed, the rate of the circulation increases as the myocardium regains its strength. In the majority of the patients it does not appear to be necessary to give digitalis during the acute stage. There is no evidence to show whether digitalis is harmful or beneficial soon after the occlusion of a coronary artery. Many clinicians do not advise giving this drug during the acute stage, for since digitalis increases both the force of the cardiac contractions and the intraventricular pressure during the contractions, it may cause a rupture of the myocardium in the area of infarction. We do not know that a case of rupture due to the use of the drug has been reported. On the other hand, digitalis may be beneficial in all cases since it is said to increase the coronary circulation and the patient's recovery depends upon an adequate circulation through the coronary arteries and their branches. It should certainly be used if the symptoms and signs of heart failure appear, or if a marked arrhythmia, either extrasystolic or fibrillatory develops. When these signs appear they are urgent enough

to warrant the intravenous injection of two to four c.c. of digifolin. The dose is calculated on a basis of one-third to one-fourth of a minim per pound of body weight, and may be repeated every two to three hours for three or four doses. If the patient has recently taken digitalis, smaller doses should be given. Subsequent doses may be regulated by the condition of the patient, but it is undesirable to reach the full therapeutic dose because of the danger of rupturing the heart or of producing toxic symptoms. We have employed the drug in this manner in two patients, watching them closely for any untoward effect, and as far as we can tell they were benefited by it. After the first few doses the intramuscular injection was substituted for the intravenous. Caution is necessary in giving digitalis soon after thrombosis occurs.

Aside from medication the administration of oxygen may sometimes be of value therapeutically. The retardation of the rate of the circulation leads to diminished oxygenation of the blood and to a deficiency in the supply of oxygen to the body tissues. This results in cyanosis, which is not marked in some cases and is probably dependent upon the slower passage of blood through the skin vessels rather than to anoxemia. In other patients cyanosis is a more prominent feature and anoxemia may exist, certainly it is favored by the presence of such factors as a slow rate of the circulation, much congestion in the lungs and some long standing pulmonary disorder, such as emphysema. By the administration of oxygen to such patients the re-oxygenation of the blood will be more com-

plete; the cyanosis will be diminished, the dyspnea will be relieved and the comfort of the patient will be increased

Absolute rest and quiet in bed to conserve the strength of the heart is of the greatest importance. Visitors should be forbidden or limited for several days following the attack. The physician should refrain from making an elaborate examination. Since the action of the heart is already encumbered, any movement of the body consequent upon a detailed physical examination increases the work of the heart unnecessarily. We can determine the condition of the patient by the quality of the heart sounds, by the character of the pulse and respirations, by the blood pressure readings, and by the condition of the abdomen. The patient should be spared the effort of feeding and turning himself in bed for two or three weeks, good nursing care is indispensable. His diet should consist of easily digested and nutritious food. During the early days of the attack the bowels are apt to become constipated as a result of large doses of morphine. It is better not to force any bowel movement for two days, then an enema may be given and one should be given daily thereafter. Laxatives should not be given until the patient is well along the road to recovery and then only in doses sufficient to produce gentle action. The patient should not have to use the bed pan more than once daily while he is in bed, slight constipation is a desirable feature.

THE LATE MANAGEMENT OF CORONARY THROMBOSIS

When the patient has recovered from the acute attack of coronary throm-

bosis, the next important consideration is the supervision of his habits of life in order to assist the heart in maintaining the circulation as near normal as possible. The time the patient may get out of bed, the extent of his activities, the use of digitalis and of other drugs which may improve the coronary circulation, and his general welfare are questions which require the utmost attention.

It is now well agreed that patients should remain in bed for at least five to six weeks for the area of infarction to heal, and that this length of time should be increased in proportion to the severity of the symptoms. This stay in bed is not sufficient for the heart to recover much of its reserve force, hence when the patient is allowed to get up he should spend only short periods of time out of the bed during the following two or three weeks. This permits the physician to see how the heart responds to the exertion. It should be remembered that the myocardium never fully recovers from the damage of infarction, and in some instances symptoms and signs of progressive failure of the heart appear soon after the patient gets up. Sudden death may occur at any time. As a rule, if convalescence from the acute stage is gradual, the myocardium regains its function sufficiently to withstand the extra work imposed upon it by the patient's getting out of bed.

When the patient is permitted more activity he should know the limitations his cardiac condition places upon him. Graduated exercises will serve a double purpose. They will enable the patient to discover how much effort he may put forth without feeling

pain, and they may possibly strengthen the heart muscle to some extent. The amount of exertion the patient can put forth without discomfort when he begins his exercise is no guide to what he will be able to do later. However, graduated exercises give him confidence in himself and since they enable him to take an intelligent interest in his welfare, he may be prevented from going to extremes, taking no precautions at all or considering himself an invalid. The amount of exercise allowed may be determined by the rate of the heart, the quality of the sounds, and whether the patient has any shortness of breath or pain referable to the precordial area. These indications also aid the physician in determining how much of his work he may resume. It is necessary to emphasize to the patient that he must rest lying down, a definite number of hours each day, the number of hours depending upon his condition.

The activities of some of the patients who survive an attack of coronary thrombosis must be very greatly curtailed since the restoration of the cardiac reserve force is insufficient to permit them to withstand much exertion. They often become discouraged because of their disability, some of them are prone to worry about themselves or their future, anxiety and fear of death will have a depressing effect upon them. If in the opinion of the physician an occasional laxity in restrictions may be allowed, it will help maintain the patient's morale. Clinical judgment again is an asset in aiding the physician to determine what is best for his comfort and happiness and for these, of course, no definite in-

dications can be given that will fit each case.

The majority of persons who survive an attack of coronary thrombosis will require digitalis soon after the acute stage is passed, or later in life. We have found that a large number of them, especially those who have had a severe attack, require it about the time they are allowed to get out of bed. Even though the heart seems to be maintaining the circulation adequately while the patient is lying in bed, we believe that the administration of digitalis at the time he is allowed to sit up strengthens the myocardium, improves the circulation and hastens the progress of the patient. When the drug is given, three to four grains of the powdered leaves each day until the signs of digitalization appear, will usually increase cardiac efficiency, then one and one-half grains given daily for as long a period of time as is necessary will usually maintain the efficiency. If this small dosage should not always be sufficient, it may be increased when symptoms and signs of decompensation appear, and decreased when the effect of the larger dose is obtained. This prolonged use of the drug increases the comfort of the patient, permits some increase in the range of his activities and rarely causes unpleasant symptoms. In all patients there are intervals when digitalis may be omitted and careful observation will determine when it should be taken again. There are intelligent patients who, after some experience, will learn to appreciate the early signs, either of too little or too much digitalis and they can guide their dose accordingly. It is interesting to observe that several

of our patients who required digitalis almost daily for twelve to eighteen months, could get along well without it after that time, while others required small doses for short periods of time.

In recent years a number of clinicians have employed the xanthine diuretics for their vasodilator effects in the treatment of heart conditions in which there have been attacks of pain. The drugs of this group most frequently employed are theobromine and its salts, and theophylline-ethylenediamine or euphylline, now known as amino-phyllin. Experiments have shown that these drugs dilate the coronary arteries, amino-phyllin possessing the greatest dilating effect. Smith, Miller and Graber³ showed that amino-phyllin increases the rate of perfusion of the intact heart from 40 to 90 per cent. The reports in the literature are unanimous in agreeing that patients who are subject to angina pectoris have the attacks less frequently and severely when taking these drugs at intervals over a long period of time, but that those who have had coronary thrombosis receive less benefit. The difference in the results obtained may be understood when we realize that the phenomena of angina pectoris can best be explained by a blood flow in the coronary vessels inadequate for the needs of the heart muscle at the moment, whereas, in coronary thrombosis there is obstruction to the flow of blood through the artery in which marked sclerosis is often found at autopsy. Obviously, we cannot expect beneficial results in these cases when the anatomic changes in the coronary arteries preclude much or any dilatation by drugs.

Our experience with amino-phyllin

has been limited to a few cases. We have given it to those patients whose initial pain continued for several days, and to other patients who had pain or tightness in the precordial area after they were allowed to resume some of their activities, but no beneficial effects were observed.

In the supervision of the patient's habits of life it is necessary not only to give attention to the manner in which the heart is functioning, but other matters pertaining to his well being must also receive attention. While stressing the importance of a rest period each day, the physician should see that the patient sleeps well each night. If there is any tendency toward insomnia we should, without hesitation, give hypnotics in sufficient doses to produce sleep. A bromide and chloral hydrate solution is the most satisfactory hypnotic, although some of the barbituric acid preparations such as adalin, amy-tal and luminal in moderate doses will act well and will not have a depressing effect, if they are not used for more than a week at a time.

Aside from the heart, the majority of these patients will more frequently complain of gastrointestinal disturbances than anything else. The patient should eat food which is easily digested. Those patients who have little or no trouble with their digestion should eat a normally balanced diet simply avoiding the foods that are digested with difficulty. Overeating should be avoided at all times. It is best for the patient if his weight is normal or near the normal. If he tends to gain weight rapidly, or if he is obese, the carbohydrates in his diet should be restricted. Many of the patients who

have had coronary thrombosis have also chronic cholecystitis. Some of them may have received medical treatment for that condition, before the thrombosis occurred, others give a history of it, but they have not received treatment. In either instance it is often necessary to prescribe a suitable diet and such drugs as are ordinarily employed in the medical treatment of cholecystitis. The response of these symptoms to this treatment is similar to that observed in other patients in that it varies, although it is usually satisfactory. Occasionally there are patients who are troubled with stasis of the intestinal contents in some portion of the intestinal tract, more frequently in the cecum or colon. This should receive appropriate treatment.

Sometimes it becomes necessary to give drugs that act as tonics, the indications for these will not be altered by the patient's having had coronary thrombosis.

SUMMARY

1 The rational treatment of coronary thrombosis depends upon a knowledge of the anatomical changes which occur in the heart following thrombosis, and of the pathological physiology accompanying these changes.

2 Morphine should be given in doses large enough and often enough to control the pain. Heat should be applied to the body of the patient. Stimulation with drugs should be avoided unless the heart sounds are very feeble and arrhythmic, the pulse is very small in volume or imperceptible, the respirations are irregular and cyanosis is prominent. Caffeine sodium

benzoate should then be given in small rather than large doses, and it should be continued as long as the condition of the patient requires it.

3 When nausea prevents the patient from taking an adequate amount of fluid and food, a small quantity of a concentrated solution of glucose should be given intravenously, and saline and glucose solution by rectum daily, and both should be continued until he can take a sufficient amount of fluids and food by mouth. Glucose is readily utilized by all the body tissues, and the saline not only prevents dehydration, but it will increase the secretion of urine which is especially desirable if the blood urea should rise to a high figure. When cerebral complications occur the patient should be kept as quiet as possible, the clinician should continue to direct his attention chiefly to the heart and the comfort of the patient.

4 It is probably better not to give digitalis soon after coronary thrombosis occurs unless signs of heart failure appear. When the indications for it arise it may be given in doses based on one-fourth to one-third of a minim per pound body weight. If digitalis is given it is better to discontinue it before the full therapeutic effect is obtained.

5 Other therapeutic measures of great value are. Absolute rest in bed until the patient is well past the acute stage. Good nursing care, a diet consisting of easily digested and nutritious food. Laxatives should not be given until the patient is well along the road to recovery, but an enema should be given daily. The administration of oxygen may be helpful to those pa-

tients in whom cyanosis is a prominent feature

6 After the patient has recovered from the acute attack, the most important consideration is the supervision of his habits of life so that the heart

may be spared any undue strain. When he may get up; how much activity he may be allowed, the use of digitalis and other drugs, his rest in bed each day and his general condition are questions that require much thought.

REFERENCES

¹BARNES, A. R., and WHITTEN, M. B.
Study of the R-T interval in myocardial infarction, *Am Heart Jr*, 1930, v, 142-171

²SOLIS-COHEN, S., and GITHENS, T. S.
Pharmacotherapeutics, materia medica and drug action, 1928, D. Appleton and Company, New York, 1508-1509

³SMITH, F. M., MILLER, G. H., and GRABER, V. C.
The effect of caffeine sodio-benzoate, theobromine sodio-salicylate, theophyllin and euphyllin on the coronary flow and cardiac action of the rabbit, *Jr Clin Invest*, 1925, 11, 157-166

Paroxysmal Tachycardia Related to the Menstrual Period*†

By J HAMILTON CRAWFORD, M D, F A C P, LOUIS H SIGLER, M D,
and H FRUCHTER, M D, *Brooklyn, N Y*

PAROXYSMAL tachycardia is a disease of extreme interest in that so many factors in regard to it remain obscure. Although electrocardiography has enabled us to localize within narrow limits the region of the heart from which the paroxysms arise, no definite conclusions have been arrived at as to the mode of initiation and maintenance of the abnormal rhythm. Many causes have been described which were related, in different individuals, to the onset of the attacks, but the common factor which these possess still remains unsolved. In spite of this, however, it seems of value to record all possible etiological aspects in the hope that eventually a solution may be found. The following cases are presented as they show a relationship between menstruation and the onset of attacks.

REPORT OF CASES

Case 1 E K, a white female, age 42, was seen first in the Cardiac Clinic of the Long Island College Hospital on February 2, 1929, complaining of palpitation, precordial pain, weakness and dizziness. She stated that in 1924 she awoke one day to find that she could not move her arms and that her

legs were very painful to touch. She called her doctor who said that she had neuritis and prescribed for her. By the next day the pain had gone and movements were free. Later in the morning she developed a severe attack of palpitation and precordial pain which required injections for its control. She became constipated and had considerable abdominal distension, while the urine was scanty. Up to 1927 she had attacks almost every other week. At this time she separated from her husband and since then the paroxysms have recurred regularly every month. As a rule they precede the menstrual period by about five days. The present attack started three days before she attended the clinic.

The patient states that in the interval between attacks she can work as a waitress without discomfort. She has some dyspnea when she climbs stairs but none on walking on the level. She experiences no palpitation or precordial pain and edema is never present. There is no gastric distress and the bowels move three times a day. The menstrual periods take place regularly every 27 days. They last four days and are profuse but dysmenorrhea is only slight. She has had some hot flashes of late but the periods have not stopped.

Previous Illnesses Patient in childhood had measles, mumps, chicken pox, whooping cough, diphtheria, scarlet fever and pneumonia. There was no history of rheumatic fever, but she frequently suffered from tonsillitis and 'growing pains'. She denies syphilis or gonorrhea.

Family History Mother and father both died of apoplexy. Patient has three children alive and well. She had frequent induced

*From the Department of Internal Medicine, Long Island College of Medicine, Brooklyn, New York

†Submitted for publication July 17, 1931

abortions She was sterilized in 1916 Patient had considerable marital difficulty before she separated from her husband She drinks a considerable amount and smokes one package of cigarettes in two days.

Physical Examination Patient was a woman of nervous disposition weighing 153 pounds There was no cyanosis or edema The tonsils had been removed and there were full upper and lower plates of artificial teeth The thyroid was not enlarged The pulse rate was 198 beats per minute and the volume was small The blood pressure was 120/100 There was marked precordial tenderness The heart was definitely enlarged, the right border being 4.5 cm from the midsternal line in the fourth interspace and the left border 13 cm from the midsternal line in the fifth interspace The sounds were closed in all areas A_2 was short and snapping There were no râles in the lungs and the liver was not enlarged The urine showed a faint trace of albumin but was otherwise negative

An electrocardiogram showed a tachycardia of supraventricular origin at a rate of 200 beats per minute It was impossible to decide whether the tachycardia was of A-V nodal origin or whether 2-1 auricular flutter was present in which one wave was buried in the ventricular complex There was slight right axis deviation The T-wave was negative in Lead 3

Treatment Vagal compression in the neck and ocular compression were without effect Patient was ordered complete rest in bed and was given quinidine sulphate six grains every four hours

Progress Notes The above attack stopped the day after she was seen in the clinic and the patient felt well again The following week she was seen in the clinic The pulse rate was 72 beats per minute and the blood pressure 120/80 The size of the heart remained the same and the sounds were closed in all areas, while A_2 was still accentuated She was ordered to take quinidine sulphate, three grains three times a day, in order to prevent further attacks, but despite this the paroxysms recurred each month The patient did not take the drug consistently, however, and was very irregular in her attendance at the clinic On one

occasion on which she appeared at the clinic in an attack, digitalis was prescribed and the paroxysm ceased after she had taken four tablets of digitalis leaves, each containing $1\frac{1}{2}$ grains Subsequently the patient attended the clinic at long intervals The attacks continued to recur each month, but were controlled by rest and small quantities of digitalis On March 11, 1931, she came to the clinic and stated that she was in the midst of an attack of greater severity than usual, which she had been unable to stop This paroxysm had been present for three days As her condition looked worse than on any previous occasion she was admitted to Long Island College Hospital Marked dyspnea was present and there was some cyanosis of the lips and malar regions Pretibial pitting was present to a slight extent The temperature was normal The pulse rate was 180 beats per minute while the heart showed the same findings as before There were moist râles at the base of both lungs and there was also marked tenderness over the upper abdomen The urine showed a trace of albumin but was otherwise negative The blood chemistry was normal as was the blood count, the white blood cells being 8,100 The Wassermann reaction was negative The electrocardiogram was identical with that taken in 1929 except that the T-wave was negative in Lead 2 as well as in Lead 3 Patient was given quinidine sulphate, six grains every four hours On March 13, she developed an attack of acute pulmonary edema from which she recovered after phlebotomy and morphine sulphate, $\frac{1}{4}$ grain All other medication was discontinued The pulse rate remained the same until March 14, when it suddenly fell to 90 beats per minute, after which it gradually slowed to about 80 beats per minute Recovery was rapid On discharge the only abnormal finding apart from the cardiac enlargement was an occasional auricular extrasystole The electrocardiogram showed nothing abnormal except slight right axis deviation Patient was ordered to take quinidine sulphate, three grains three times a day The following week the patient appeared at the clinic in another attack She said that this was the only time for many years that an attack had recurred after

such a short interval. As no beds were available in hospital and as the symptoms were not as severe as with the last attack she was instructed either to go home to bed and take tablets of digitalis leaves, $1\frac{1}{2}$ grains three times a day, or to go to a City Hospital. Since then patient has not returned to the clinic and cannot be located.

Case 2 S. M., a female 17 years of age, was admitted to the Coney Island Hospital on February 15, 1930, complaining of severe palpitation and precordial pain. The patient stated that she had had frequent attacks of this nature. The first attack preceded by two days her first menstruation at the age of $13\frac{1}{2}$ years, and since then she has had an attack practically every month at the time of the menstrual period. Only two attacks were unrelated to menstruation and both followed extreme excitement. At the onset of an attack the patient experienced a sensation of momentary stoppage of the heart. Likewise the cessation of the paroxysm was abrupt. Until the present attack the paroxysms have lasted only a few hours and as a rule a day of normal cardiac activity has intervened before the onset of menstruation. During a paroxysm the patient suffered from palpitation, precordial pain, and weakness, but as a rule dyspnea was not marked. Vomiting occurred on some occasions and sometimes caused the attack to terminate. In the interval between attacks the patient had no symptoms except slight dyspnea on exertion and at times precordial pain. The menstrual periods occur every twenty-eight days, last two or three days, and the patient does not suffer from dysmenorrhea.

The present attack began on February 13, but unlike the previous attacks, persisted longer. Signs of circulatory failure began to appear and in consequence the patient was removed to the hospital.

Previous Illness At the age of ten the patient fainted in school, and a physician, who was consulted, stated that she had heart disease. There was a history of repeated tonsillitis up to the age of $2\frac{1}{2}$ years, at which time tonsillectomy was performed, but there was no other history suggestive of rheumatic infection. She had measles and whooping cough in childhood. In 1924

a brother was referred to the clinic of Dr. Givan, at the Long Island College Hospital, suffering from congenital syphilis. In consequence of this, Wassermann tests were performed on all the family and our patient was found to have a two plus reaction. Arsphenamine treatment was instituted but the patient had a severe reaction after each of six injections so it was decided to discontinue the treatment. She was then re-referred to the Cardiac Clinic for further care. The clinic report showed that at that time she complained of severe precordial pain, dyspnea, and palpitation. The heart was enlarged and a systolic murmur was present at the apex while the second sound at the pulmonary area was much accentuated. The patient later developed a presystolic murmur at the apex. A diagnosis of mitral stenosis and insufficiency was made. In 1926 she left the clinic, the Wassermann reaction being still two plus, and she received no medical attention until her admission to the hospital.

Family History The parents and two sisters appear healthy. One brother has signs of congenital lues. The mother had one miscarriage.

Physical Examination The patient was a pale young girl with cyanosis of the nail region, lips, and extremities, but no edema. None of the stigmata of congenital syphilis was present. There was left lateral scoliosis. The thyroid was slightly enlarged, and the eyes showed slight prominence. There was marked pulsation of the vessels of the neck, both arterial and venous. The tongue was slightly furred and the teeth were in good condition. A few tonsillar tags were seen but these did not appear to be infected. The temperature was 102°F . The pulse was very rapid, of small volume, and capillary pulsation was present. The blood pressure was 114 systolic and 52 diastolic. The heart rate was 250 per minute. There was a diffuse pulsation all over the precordium and a systolic thrill, which was maximal over the mitral area, was felt over the greater part of this region. The apex was in the 6th interspace, 11.5 cm. from the midsternal line. The measurements of the right and left borders of the heart in the fourth and sixth interspaces respectively were 15 cm.

and 120 cm On account of the rapidity of the heart it was difficult to decide whether any murmurs were present The second sound at the pulmonary area was accentuated The bases of the lungs showed a few moist râles, but there was no enlargement of the liver

Laboratory Data Red blood cells, 3,400,000, hemoglobin, 70 per cent, white blood cells, 18,200, with 80 per cent polymorphonuclear cells Urine sp gr, 1.032, acid, albumin, ++, sugar, negative, no casts The blood Wassermann reaction was negative on several occasions An electrocardiogram showed a heart rate of 250 beats per minute due to a tachycardia of A-V nodal origin The R wave was notched in leads 1 and 2 and slurred at the top in lead 3 X-ray examination of the heart showed a definite enlargement which was predominantly left ventricular The cardiac index was 0.56 There was slight prominence in the region of the left auricular appendix

Treatment Vagal compression in the neck and ocular pressure produced a slight slowing of the heart rate but failed to restore the normal rhythm On February 15, the day of admission, fluids were restricted to 1000 cc per day, an ice bag was applied to the precordium, tincture of digitalis, 20 minims, was given three times a day, and quinidine sulphate, three grains, was administered every four hours, day and night On February 16, the latter was increased to six grains every four hours, and on February 17, eight grains every four hours

Progress Notes The patient's condition remained the same until February 18, except for a slight increase in the size of the heart and the appearance of more râles at the bases of the lungs Both physical examination and electrocardiograms showed that a gradual slowing of the heart rate to 190 beats per minute took place during this period No symptoms of toxicity due to quinidine were observed At 8.30 p.m. on February 18, three days after admission, normal rhythm was suddenly resumed An electrocardiogram taken immediately after the resumption of normal rhythm showed normal sinus rhythm with a heart rate of 95 beats per minute The P-R interval was 0.13 sec R was slightly notched in leads

1 and 3 and slurred in lead 2 T was negative in all leads The temperature which had become much lower on the second day in the hospital now became normal There was a rapid improvement in the patient's condition The marked pulsation in the neck and in the precordial region disappeared, although a diffuse pulsation was still present in the region of the apex The size of the heart decreased, the left border being 10.5 cm from the midsternal line in the sixth interspace It was now possible to analyse the character of the heart sounds At the mitral area the first sound was preceded by a presystolic rumble and followed by a loud systolic murmur, while the second sound was followed by a slight diastolic murmur Just above the apex the second sound was reduplicated At the aortic area the sounds were faint, but in the second and third left interspaces, close to the sternum, a diastolic murmur was heard which was faintly transmitted down to the lower end of the sternum The râles at the lung bases rapidly disappeared

An electrocardiogram taken on February 28, just before discharge from hospital showed normal sinus rhythm with a heart rate of 85 beats per minute The P-R interval was 0.13 sec R was notched in lead 1 The R-T interval was curved and slightly depressed in leads 1 and 2 while T was negative in lead 3 At this time the basal metabolic rate was estimated and was found to be normal

The patient was discharged from the hospital with instructions to take quinidine sulphate, three grains, three times a day, for three days before the menstrual period However, about four days before the next period the patient, as a result of excitement, developed an attack which lasted several hours She was then told to take quinidine for a week previous to menstruation, but on the day preceding this period she had another attack which lasted ten minutes At the time of the next period an attack, which lasted twenty-four hours, took place two days preceding menstruation despite the administration of quinidine Quinidine was then given continuously in the same dosage, since which time there has been no recurrence

DISCUSSION

The outstanding feature, in these cases, is the relationship of the onset of the paroxysms to the menstrual periods. References to menstruation as one of the causal factors in precipitating attacks of paroxysmal tachycardia are infrequent. Vaquez and Pezzi¹ reported a case of paroxysmal tachycardia in a woman, with no evidence of organic heart disease, in whom the attacks were always related to the onset of menstruation. Paroxysms did not occur at every period but gradually increased in frequency and duration until the menopause was reached when they recurred at short intervals. Savini² studied a series of cases of this nature and concluded that the thyreo-genital systems play an important part in the production of attacks of paroxysmal tachycardia. He believes that these systems are mutually antagonistic, i.e., hypogenitalism produces hyperthyroidism which then tends to induce paroxysmal tachycardia. He states that attacks commonly start at puberty or the menopause and in the interval are related to the menstrual periods. Even in individuals in whom the attacks occur unrelated to menstruation more severe paroxysms are experienced if they occur at this time. He states that cases were aggravated by the administration of thyroid extract and were relieved by ovarian extract in women or by testicular extract in men. We feel, however, that at least the latter statement is contrary to the general experience while the hypothesis as a whole lacks adequate proof. Martinez³ studied thirty-one cases and he found that twenty-one of these had organic or functional disease of the

sympathetic or endocrine systems, either gross thyroid disease, genital disease, or indications of a disequilibrium of these systems. The determining factor in the production of the attacks was, as a rule, the prodromal symptoms of the menses but in some instances it was due to a delay in the onset of menstruation. Geraudel⁴ described a case in which attacks of paroxysmal tachycardia started at puberty and recurred every month at the time of the period. Lutier⁵ also reported the case of a young woman who suffered from exophthalmic goiter with irregular menstruation, in whom the first attack took place on the eve of a period, while subsequent paroxysms occurred most often at the time of menstruation. We have recently seen a young woman who was subject to attacks of paroxysmal tachycardia at long intervals and who showed no signs of organic heart disease. This patient became pregnant and since then the attacks have become more frequent and severe. Meyer, Lackner and Schochet⁶ have described two cases which they have studied and six cases from the literature, in whom attacks of paroxysmal tachycardia took place either during pregnancy or labor. One case was subject to attacks before she became pregnant, but there was an increase in their frequency during the pregnancy.

The causes which produce attacks of paroxysmal tachycardia are many and often obscure. There seems little doubt, however, that in our cases the provocative factor was the changes produced in the body by menstruation. It seems doubtful whether the thyroid in the absence of obvious thyroid dis-

ease, as in these cases, has as much responsibility for the attacks as some of the authors quoted above seem to think. It seems to us more probable that the attacks were due to some alteration in the activity of the sympathetic nervous system at the time of menstruation. The mechanism by which a change in the action of the sympathetic nervous system on the heart could induce an attack of paroxysmal tachycardia is at present unknown. It is possible that it may increase the sensitivity of some focus outside the sino-auricular node so that it emits impulses which control the heart. Or it may be that it causes an extrasystole which strikes the heart in a critical phase so that a circus movement is initiated and thus the abnormal rhythm perpetuated. Further evidence in favor of an alteration in the activity of the sympathetic system, as a cause of paroxysmal tachycardia, is that in many individuals, subject to attacks of this nature, the precipitating factor is excitement. On the few occasions in which the attacks in the second patient were unrelated to menstruation the provocative factor was great excitement, while in the first case the attacks were much more frequent when marital difficulties were present.

It is doubtful how great a part the pathological processes in the hearts of these patients played in the causation of the attacks. It is well known that paroxysmal tachycardia occurs in some cases of organic heart disease. On the other hand many who present no evidence of organic heart disease suffer from these attacks while in only a relatively few cases of organic heart disease do they occur. It may be that pathological changes in the heart predispose to some extent to the paroxysms but it seems as if some other influence were the important factor in initiating the attacks. In the cases presented the evidence of the relation of the onset of the paroxysms to menstruation is very striking and one feels that this provided the necessary stimulus.

SUMMARY

Two cases of paroxysmal tachycardia of supraventricular origin are described in one of which the attacks commenced at puberty and recurred at each subsequent menstrual period. In the other the paroxysms commenced later in life. In the early stages they occurred at frequent intervals, but for a period of years they have almost invariably had a definite relation to the menstrual period.

REFERENCES

- ¹VAQUEZ, H., and PIZZI, C. Tachycardie paroxystique de type auriculaire, Bull et mem Soc méd d hop de Paris, 1912, xxxiii, 360-370.
- ²SAVINI, I. Études sur la tachycardie paroxystique (étiologie, pathogénie formes, cliniques traitement), Arch d mal du cœur, 1912, v, 689-716.
- ³MARTINEZ, G. N. Recherches étiologiques sur la tachycardie paroxystique, Arch d mal du cœur, 1925, xviii, 292-300.
- ⁴GIRARDI, E. Études sur la tachycardie paroxystique, tachycardie paroxystique et flutter, Arch d mal du cœur, 1928, xxi, 273-287.
- ⁵LATHIER, A. Crises de tachycardie de Basedow fruste chez une jeune fille mal réglée, Presse méd, 1929, xxxvii, 492.
- ⁶MEYER, J., LACKNER, J. E., and SCHUCHT, S. S. Paroxysmal tachycardia in pregnancy, Jr Am Med Assoc, 1939, xcix, 1601-1604.

The Coincidental Occurrence of Diabetes Mellitus and Pernicious Anemia*†

Report of Two Cases

By CHARLES SHOOKHOFF, M D, *Brooklyn, N Y*

DIABETES mellitus is mentioned by Giffin and Bowler¹ as being one of the diseases which may be associated with anemia. Joslin² in a series of six thousand diabetics observed five instances in which diabetes mellitus and pernicious anemia co-existed. Adams³ found three such cases in a five year period, during which time two thousand patients with diabetes mellitus and one thousand patients with pernicious anemia were observed. Wright⁴ found two instances out of 475 patients with diabetes mellitus and 84 patients with pernicious anemia. Goudsmit⁵ reports five cases out of a total of 1063 cases of diabetes and 379 cases of pernicious anemia observed at the Netherland Clinics. Other instances of the coincidental occurrence of these diseases have been reported by Parkinson,⁶ Yong (cited by Joslin², Schumann⁷, Arntzen⁸, Hitzrot⁹, Berghausen¹⁰, Meulengracht¹¹, Bowen¹², and Baumgartner¹³). Recently Root¹⁴, in a résumé of this subject gathered together 48 cases, thirteen of which were found out of seven thou-

sand diabetics. These latter figures include Joslin's case.

The cases reported below are of interest not only because of the rarity of the concomitant occurrence of diabetes mellitus and pernicious anemia, but also because it is thought that with the increase in the number of case reports in which the specific methods of treatment for both the diabetes mellitus and pernicious anemia have been used, a better idea as to the possible relationship or the effect of the presence of one disease on the course of the other disease may be obtained.

CASE REPORTS

Case I Female, white, 58 years of age, was first seen in December, 1928.

Complaints Weakness, loss of appetite, loss of sixteen pounds in one year, sweats, hot flushes, and edema of the ankles, one month duration.

History Mother and father are dead, age and cause unknown. One brother has diabetes and high blood pressure and one sister has a high blood pressure. Patient had measles at five years of age and no other illnesses. Menopause at the age of forty-nine years.

Physical Examination Well nourished female of the sthenic type. Weight 166½ lbs, height 64¼ ins. Definite glossitis present. Eyes reacted to light and accommodation. Lungs normal. Circulatory system: blood pressure 160/75; regular sinus rhythm.

*From The Jewish Hospital of Brooklyn and The Greenpoint Hospital of Brooklyn, N Y.

†Received for publication, June 1, 1931.

basilar vessel line percussed as widened to the left, A-2 accentuated and musical, definite aortic configuration with an enlargement of the left ventricle, heart sounds of good quality, no carotid sheath reflex vagal reaction noted, the left leaf of the diaphragm high standing Abdomen spleen palpable one finger below the costal margin, abdomen otherwise negative Reflexes normal Varicose veins of lower extremities, no edema No loss of vibratory sense

Laboratory Data Urinary sugar 4.65%, fasting blood sugar 160 mgms per 100 cc of blood serum, Blood hemoglobin, 60%, red blood cells, 1,400,000, white blood cells, 4,400, 72% polymorphonuclears, 26% lymphocytes, 1% eosinophiles, macrocytosis

Diagnosis Essential hypertension, diabetes mellitus and a possible pernicious anemia

Patient became sugar free on diet and twenty units of insulin daily, and after having been given the equivalent of 200 grams of liver daily her blood count was 3,100,000 with 65% hemoglobin

In June, 1929, the patient reappeared with symptoms due to increasing anemia She was admitted to the Jewish Hospital of Brooklyn complaining of increasing weakness, hot flushes, profuse sweats, edema of the legs, pain, weakness and parasthesias in both lower extremities

Physical Examination There was now a marked lemon-yellow pallor which had increased since the last time she was observed Glossitis Tonsils and pharynx slightly infected Lungs a few crepitant râles at both bases which disappear on breathing Heart as on previous examination, blood pressure 155/80 Abdomen the liver was one fingerbreadth below the costal margin, hard, not tender, spleen palpable Reflexes slightly diminished The vibratory sense was definitely diminished in the right leg and entirely lost in the left

Laboratory Data Urinary sugar, 1%, fasting blood sugar, 166 mgms to 100 cc blood serum, CO₂ combining power, 53.6, urea nitrogen, 12.5, sugar tolerance

	8 30	9 30	10 30	11 30
Blood	171	410	444	410
Urine	0	0.25	6.6	10%
Cholesterol	256 mg			

Blood hemoglobin, 55%, red blood cells, 2,180,000, white blood cells, 4,800, 45% polynuclears, 47% lymphocytes, 5% mononuclears, blood platelets, 120,000, bleeding time one-half minute, coagulation time two minutes, anisocytosis and poikilocytosis, polychromasia marked, macrocytosis, one megaloblast in 100 white blood cells, reticulation, 5%, icteric index, 93, Van den Bergh, indirect, one unit Gastric analysis free acid, 5, 0, 0, 3, total acidity, 10, 28, 42, 45 Wassermann and Kahn tests negative Temperature and pulse rate were within normal limits

Treatment Diet 60 grams carbohydrates, 60 grams proteins, 70 grams fats Ten units insulin twice a day Transfusion, 240 cc, group "O" donor The equivalent of 300 grams of fresh liver was given daily

The patient became sugar free in a short time and left the hospital against advice While the diabetes seemed to be controlled, the anemia did not improve and a blood count on June 30, 1929, showed a hemoglobin of 58% and red blood cells, 2,100,000 At this time she developed an upper respiratory infection, a herpes labialis and a febrile reaction which lasted for a few days We again advised hospitalization and she was admitted to the Greenpoint Hospital on July 2, 1929 Her physical findings on this admission were not different than on previous examinations, except that she looked more anemic Blood pressure was 160/80

Laboratory Data July 3, 1929 urine negative, fasting sugar, 77 mgms, blood urea, 28, Wassermann, negative Blood hemoglobin, 50%, red blood cells, 2,110,000, white blood cells, 4,900, 52% polynuclears, 40% small lymphocytes, 8% transitionals Gastro-intestinal roentgenological examination revealed no abnormalities

On July 9, the patient was given a transfusion of 250 cc of blood, group "O" donor Liver extract was given also, and she continued with her insulin She was discharged from the Hospital on July 18, 1929, sugar free A blood count on November 13, 1929, showed hemoglobin, 80%, and red blood cells, 4,230,000

Subsequent communications from patient and her physician informed us that while her anemia seemed to remain under control

on the liver diet, more insulin was required to control her diabetes

COMMENT

The diagnosis of diabetes is definite. The diagnosis of pernicious anemia is based on the blood picture.

(A) High color index, macrocytosis, etc., high icteric index, positive indirect Van den Bergh test, and relative lymphocytosis,

(B) the clinical findings of glossitis, cord symptoms, large spleen, lemon-yellow color,

(C) absence of gastro-intestinal abnormalities, bleeding or any other cause for the anemia.

This patient's reaction to treatment is somewhat similar to Hitzrot's⁹. The diabetes was at first more easily, and her anemia less easily, controlled. Subsequently, after two transfusions and liver therapy, the patient entered a remission, but the diabetes became more pronounced and more insulin was required to control it.

Case II Female, white, age 61 years. Admitted to the Jewish Hospital of Brooklyn, surgical service of Dr. William Linder, on September 18, 1929.

Chief Complaints Attacks of severe pain in the right upper quadrant, temperature, nausea, loss of appetite, constipation, loss of sixty pounds in eight months.

History Family history is negative. Patient had a dry pleurisy in 1922, and has had diabetes for eight years.

Present Illness Eight months ago she suffered her first severe attack of pain in the abdomen, radiating to the right upper quadrant, has since had repeated attacks, particularly at night. Two months ago after a particularly severe attack, jaundice and clay colored stools were noticed. Patient has been losing weight, has a poor appetite and has been complaining of increasing weakness.

Physical Examination Temperature 101°. Female with a yellowish pallor, apparently has lost some weight. Eyes react to light and accommodation. Glossitis present. Heart and lungs negative. Abdomen some tenderness in the right upper quadrant, liver and spleen not palpable. No abnormal neurological findings.

Laboratory Data Urinary sugar 12%, fasting blood sugar, 241 mgs sugar in 100 cc blood serum, CO₂ combining power, 50.7. Blood hemoglobin, 45%, red blood cells, 900,000, white blood cells, 8,600, 74% polymorphonuclears, 20% lymphocytes, 6% large mononuclears.

Treatment was instituted by giving seven units of insulin three times a day and 500 cc of a 5% solution of glucose intravenously daily.

On September 21, the hemoglobin was 37%, red blood cells, 1,300,000, white blood cells, 2,500, 67% polymorphonuclears, 26% lymphocytes, 2% mononuclears, 1 eosinophile, 1 basophile, myelocytes, 2, metamyelocytes, 0.666, myeloblasts, 0.33, anisocytosis, polychromasia and poikilocytosis marked, many macrocytes, few giantocytes, reticulation, 3%, icteric index, 7.2, bilirubin plus, indirect, one unit blood.

On September 23, urinary sugar, 0.5%, no acetone, fasting sugar 120 mgs to 100 cc blood serum, CO₂ combining power, 57.4. On September 24, a transfusion of 500 cc blood, group "O" donor, was given and liver extract, one vial every three hours. On September 25, a 5% glucose retention enema, was ordered, six ounces three times a day. On September 29, the patient had a fasting sugar of 150 mgs per 100 cc blood serum, CO₂ combining power, 60.2. On September 30, gastric analysis showed no free hydrochloric acid. The patient was given dilute hydrochloric acid, twenty mms between meals.

At this time temperature had dropped to normal. The patient was sugar free on a diet of 100 grams carbohydrates, 60 grams proteins, and 150 grams fats. No further gall bladder attacks were experienced. Hemoglobin was 45%, red blood cells, 2,070,000, reticulation, 1%.

On October 7, 1929 the urine was normal, no acetone. Blood examination showed

55% hemoglobin and red blood cells, 3-040,000. There had been no further gall bladder attacks and the patient was discharged.

Final Diagnosis Pernicious anemia, diabetes mellitus, chronic cholecystitis, and chronic cholelithiasis.

This patient was subsequently readmitted to the Hospital for a blood transfusion because of her failure to react to liver therapy. At this time her diabetic condition was well under control.

COMMENT

The diagnosis of both the diabetes mellitus and pernicious anemia is clear in this case.

The diabetes seemed to respond very readily to insulin despite a fairly liberal diet, while the anemia did not respond as well to liver therapy. Further blood transfusions were necessary at a time when the diabetic condition was under control.

DISCUSSION

In a study of anemia associated with pancreatic disease, Chvostek¹⁵ concluded that severe anemias dependent only upon disease of the pancreas may exist. The onset of the anemia, the absence of cachexia, the absence of symptoms referable to gastro-intestinal disease, and finally, the presence of lesions in the pancreas only, at post-mortem, were the reasons for the assumption of a pancreatic anemia. He thought such anemias were hemolytic in nature and suggested the possibility of a pancreatic disease being the underlying factor in some cases of pernicious anemia.

Giffin and Bowler¹ stated that glycosuria, if not true diabetes, may be due to severe anemia. Meulengracht and Iversen¹⁶ found in pernicious ane-

mia an increase in the blood sugar levels and a delay in their return to normal. Strauss¹⁷, however, found no glycosuria in six cases of pernicious anemia after the administration of 100 grams of glucose.

Greene and Conner¹⁸ showed that liver function in the primary anemias is not often disturbed. They found no retention of phenoltetrachlorophthalein in nine out of twelve cases of pernicious anemia studied. In two patients a very slight retention of dye was noted. There was a definite diminution in excretion of the dye in only one patient.

These observations do not clarify the situation. Pancreatic disease may cause anemia, anemia may cause disturbance of carbohydrate metabolism. On the other hand, severe pancreatic disease without anemia is frequently observed, while patients with severe anemia may have a normal carbohydrate metabolism and normal pancreatic and liver function.

Both diabetes mellitus and pernicious anemia have at present a specific therapy, a therapy dependent probably in both instances on an insufficiency of internal glandular secretion. The results of the use of these specific forms of treatment in uncomplicated cases have been excellent.

H. Blotner and W. B. Murphy¹⁹ found that liver, which had previously been contra-indicated as a food in diabetes because of its high glycogen content, when administered to diabetic patients, showed a very beneficial effect on their blood sugar curves. They showed that certain liver fractions which are ineffective in the treatment of pernicious anemia have a definite

beneficial effect on the blood sugar curves of diabetic patients. Von Varga²⁰ obtained good results with insulin and combined liver and insulin therapy in eight cases of severe pernicious anemia. He believed that insulin was certainly not contra-indicated in severe anemias. Adams³ observed a definite decrease in the effectiveness of insulin in lowering the blood sugar in profound anemia. No high liver diets were then given.

The response to specific therapy in those patients in whom the two diseases co-existed varied widely. The anemia with marked cord symptoms preceded the diabetes in Baumgartner's¹³ patient by one year. The diabetes came at a time when the anemia was well under control. There was a marked improvement in both diseases upon the use of liver, insulin and diet. Yong's² patient had diabetes for four years and had been given as high as ninety units of insulin per day before the primary anemia was discovered. She responded nicely to the combined treatment. Arntzen's⁸ patient showed a decided improvement in both the diabetes and pernicious anemia on the combined treatment. Goudsmit's⁵ patient showed an increase in her sugar tolerance when put on a liver diet. The diabetes was mild or not in evidence in Hitzrot's⁹ patient during the height of the anemia, but reappeared during the remission of the pernicious anemia which had responded to a Minot-Murphy regime. In our Case I the diabetes seemed to respond readily to treatment, diet and insulin, while the pernicious anemia was more difficult to control. Not much improvement in the anemia

was noted on concentrated liver diet until after two blood transfusions were given, from then on there was a definite improvement on liver feedings. After the anemia was controlled the diabetes became more severe and more insulin and a stricter diet became necessary. Meulengracht's¹¹ patient had pernicious anemia, hyperthyroidism and diabetes mellitus. The anemia reacted well to the liver diet, and at the height of her remission the patient complained of thirst and loss of weight and was readmitted to the clinic with a marked diabetes. While the anemia was controlled by the liver therapy, the diabetes was not so easily managed, at a time when this patient had a hemoglobin of 91 per cent and 4,200,000 red blood cells, she had a fasting sugar of 309 mgs of sugar per 100 c.c. of blood serum. Bowen¹² found no evidence of a blood sugar lowering action of liver in the case he reported. The diabetes in his patient became much more severe during a two month period during which she was under observation. Berghausen's¹⁰ patient, a female 70 years of age, had had diabetes since 1913, symptoms of the pernicious anemia appeared in 1928, liver therapy or antidiabetic treatment had no effect upon the pernicious anemia. In our Case II the diabetes had existed for eight years prior to the onset of the pernicious anemia and was always easily controlled by diet and later by insulin. The diabetes continued mild after the onset of the pernicious anemia. The anemia however did not seem to react as well to liver diet and transfusion as is usually the case with uncomplicated pernicious anemia.

Root¹⁴ states that good results were obtained with insulin, liver, or a potent substitute, and a diet rich in vitamins.

The rarity of the occurrence of the combination of these two diseases which individually are common, this maze of partially contradictory experimental and clinical data and response to specific treatment, makes tenable the supposition that these diseases are not inter-related and that their occurrence in the same patient is entirely coincidental.

Diabetes is frequently associated with, and by some observers is considered the cause of, coronary sclerosis. Angina pectoris on that pathological basis is not an infrequent symptom in diabetes. Herrick²¹ and others have described an angina pectoris symptom complex in patients with severe anemia, and ascribed it to the insufficient and poor cardiac muscle blood supply. It is of interest in the light of these facts, that in none of the cases reported in which both diabetes mellitus and pernicious anemia co-existed has any mention been made of an angina pectoris symptom complex being present.

SUMMARY

Two cases of the coincidental occurrence of diabetes mellitus and pernicious anemia are reported, one in whom the diabetes antedated the pernicious anemia by eight years, and the other in whom both diseases were found simultaneously. Liver and insulin were given to both patients. In Case I the diabetes became more severe at a time when the patient had entered into a remission of the anemia, in Case II the anemia did not respond well to specific treatment, while the diabetes was always easily controlled by insulin and diet.

No relationship seems to exist between pernicious anemia and diabetes, nor does the presence of one disease affect the course of the other in a characteristic manner.

Results of specific therapy, when a sufficiently large number of patients having both diseases have been treated, may give some information as to the relationship of these diseases. In the few cases so far studied uniform results have not been obtained.

We wish to thank Dr. William Linder for his kindness in permitting us to report Case II.

REFERENCES

- ¹ GIFFIN, H. Z., and BOWLER, J. P. Diseases which may be associated with pernicious anemia, *Minn. Med.* 1923, vi, 13-16.
- ² JOSLIN, E. P. The treatment of diabetes mellitus. 1928. Lea and Febiger, Philadelphia and New York, p. 761.
- ³ ADAMS, S. F. Three cases of pernicious anemia and diabetes mellitus with a note on the apparent ineffectiveness of insulin in the presence of profound anemia, *Med. Clin. No. Am.*, 1925, viii, 1163-1170.
- ⁴ WRIGHT, F. R. Diabetes mellitus and pernicious anemia, *Clifton Med. Bull.* 1925, xii, 64-67.
- ⁵ GOLDSMIDT, J. Over de combinatie diabetes-perniciëuse anaemie, *Nederl. tijdschr. v. geneesk.*, 1930, lxxiv, 1447-1463.
- ⁶ PARKINSON, J. A case of pernicious anemia terminating in acute diabetes, *Lancet*, 1910, ii, 543-546.
- ⁷ SCHUMANN, C. Pernicious anemia with diabetes, leukemia in daughter. *Jr. Am. Med. Assoc.*, 1925, lxxv, 677.
- ⁸ MAYER, J. D. Aplastic anemia. II.

- Pernicis anemi og diabetes mellitus, Norsk mag f laegevidensk, 1930, xci, 489-495
- ⁹HITZROT, L. H. Coincident diabetes mellitus and pernicious anemia, with report of a case, Am Jr Med Sci, 1929, clxxvii, 213-219
- ¹⁰BERGHAUSEN, O. Coexisting diabetes mellitus and pernicious anemia, So Med Jr, 1929, xxii, 594-595
- ¹¹MEULENGRACHT, E. Morbus Basedowii und perniziose Anämie, Klin Wchnschr, 1929, viii, 18-21
- ¹²BOWEN, B. D. Comparative effect of liver and liver extract on diabetes in a case of combined pernicious anemia and diabetes, Jr Am Med Assoc, 1930, xcv, 30
- ¹³BAUMGARTNER, E. A. Improvement in neurological findings in pernicious anemia after liver feeding, report of a case, Clifton Med Bull, 1930, xvi, 1-5
- ¹⁴ROOF, H. F. Diabetes and pernicious anemia, Jr Am Med Assoc, 1931, xcvi, 928-933
- ¹⁵CHVOSTEK, F. C. Pankreas- Anämie- Hämochromatose, Wien klin Wchnschr, 1918, xxxi, 121-130
- ¹⁶MEULENGRACHT, E., and IVERSON, P. Der Blutzucker bei perniziöser Anämie, Deutsch Arch f klin Med, 1925, cxlviii, 1-9
- ¹⁷STRAUSS, H., et al. Metabolism and practical medicine, 1907, W. T. Keener and Company, Chicago, ii, 354
- ¹⁸GREENE, C. H., and CONNER, H. M. Diseases of the liver V. A comparative study of tests for hepatic function in certain disease of the hematopoietic system, Arch. Int Med, 1926, xlviii, 167-185
- ¹⁹BLOTNER, H., and MURPHY, W. P. The effect of liver on the blood sugar level, Jr Am Med Assoc, 1929, xcii, 1332-1336
- ²⁰VON VARGA, L. Insulin bei der Behandlung der perniziösen Anämie, Deutsch med Wchnschr, 1929, lv, 433-434
- ²¹HERRICK, J. B. On the combination of angina pectoris and severe anemia, Am Heart Jr, 1927, ii, 351-355

The Significance of Meningeal Permeability*†

By S. KATZINILBOGEN, M.D., F.A.C.P., *Baltimore, Md.*

BY "meningeal permeability" one designates the function regulating the exchanges between the general circulation and the cerebrospinal fluid. In recent literature this function is commonly described under the term "hematoencephalic barrier" or "barrier" between blood and fluid.¹ This new terminology² appears to be the more appropriate one, for, according to the prevailing, if not unanimous opinion, not only the meninges, but also various other structures of the cerebrospinal system and particularly the choroid plexus, take part in the function which has been inadequately ascribed to the meninges exclusively.²

The subject of this communication offers a wide range of topics which may be of interest to the biologist at large. For the discussion of to-day I chose two topics which, I think, deserve the attention of the medical man. These topics are: First, the diagnostic value of the "meningeal permeability." Second, its significance from the standpoint of therapeutics. With regard to diagnosis, it may be asserted that the actual knowledge on the exchanges be-

tween blood and cerebrospinal fluid proves to be helpful, in allowing a better approach to an adequate evaluation of the composition of the fluid. In a personal contribution to this subject, I found that the increase of the glucose content in the blood of rabbits, induced either by intravenous injections of glucose or by hypodermic administration of adrenalin, is followed by a rise of glucose in the fluid.³ Certain clinical observations on the distribution of glucose between blood and fluid are no less demonstrative. It is common knowledge that in the periods of epidemic encephalitis in 1917 to 1921, hyperglycorachia was commonly considered an important symptom of this disease.⁴ Subsequent determinations of sugar in blood and fluid withdrawn simultaneously in encephalitis and in various other diseases have, however, demonstrated that in a great many cases hyperglycorachia is proportionate to hyperglycemia,⁵ in these cases the high fluid glucose is evidently of no more significance than the high blood glucose itself. From these experimental and clinical investigations the following inference may be made: The amounts of glucose and, suggestively, of other diffusible components of the cerebrospinal fluid should not be estimated *per se* as absolute values, but as compared to the concentration

*Presented at the Fifteenth Annual Clinical Session of The American College of Physicians, March 27th, 1931, Baltimore, Md.

†From the Henry Phipps Psychiatric Clinic (Department of Internal Medicine), Johns Hopkins Hospital, Baltimore, Md.

of these components in the blood. On the other hand, certain data available in the literature have brought to light the following concept: various pathological conditions, mainly those associated with meningeal involvement are accompanied by an increase of the barrier permeability.⁶ In a personal study on the therapeutic effects of aseptic meningitis in epidemic encephalitis, provoked by intraspinal injections of casein, a distinct increase of the permeability to nitrate given by mouth was found, an increase which appeared to parallel the meningeal congestion, if not to follow proportionally, its intensity.^{7, 8} These findings suggest the contention, that discrepancies between the contents of diffusible components in blood and fluid may be plausibly ascribed to an altered function of the hematoencephalic barrier. Finally, in synthesizing the data so far recorded, I feel justified in venturing the following conclusion: Both experimental and clinical investigations contribute strongly to the view, that the concentration of the diffusible elements of the cerebrospinal fluid depends partly on their concentration in blood, and partly on the permeability of the "barrier" between blood and fluid.

For diagnostic purposes the function of the barrier has been tested, in the last three decades, in two ways, which have the common character of investigating the passage from the general circulation into the cerebrospinal fluid. The passage of blood constituent, such as hemolysins (Kafka and Weil), urea, sugar, chlorides (Derrien), syphilitic antibodies (Dujardin) and of substances introduced into the general circulation, such as nitrate (Mestre-

zat) iodine (Sicard, Osborne), uranine (Kafka, Schonfeld),⁹ etc. These tests have rendered service in determining an increased permeability in various pathologic conditions of the cerebrospinal system, particularly in those associated with involvement of the meninges. These tests are however charged with failure to give direct information as to normal or decreased permeability. The bromide permeability test devised by Walter⁹ six years ago is credited with filling this gap, that is, making possible the study of the normal and decreased, as well as the increased function. The test is performed by the following procedure: The subjects are given sodium bromide by mouth, 0.6 per kilogram weight, in twenty-four hours for five days. On the sixth day lumbar and venous punctures are performed successively and the content of bromide is determined in both blood and fluid. In accordance with most investigators, the normal ratios between the amounts of bromide in blood and fluid, called permeability quotients, lie within the limits of 2.9 to 3.3. These figures were considered normal standards in the studies so far carried out in this clinic. The bromide permeability test was used in various diseases, such as nephritis, diabetes, tuberculosis, skin diseases, etc., rather sporadically (Sunderhauf, Leopold). The bulk of studies is to be found in nervous and mental diseases. Perusal of the literature gives the distinct impression that the permeability of the barrier between blood and cerebrospinal fluid is raised in organic psychoses, particularly in general paresis and cerebral arteriosclerosis; that it is diminished in schizophrasia and within nor-

mal limits in manic depressive patients² The results obtained in a study of 188 patients, carried out in the Phipps Clinic, in collaboration with the City Hospital, are somewhat different The graphic presentation of our findings shows the following essential features (Chart I):

1 In each psychotic group the prevalent number of cases has a normal permeability It is worth noting that the percentage of normals is strikingly high in organic psychoses and in schizophrenia, that is, in the two psychotic groups in which, as mentioned above, an essentially abnormal permeability was found by most investigators

2 In our experience, however, an increased permeability was observed more frequently in organic psychoses, than in any other psychotic group, and a low permeability was found in a relatively high percentage of cases with schizophrenia, as compared to organic psychosis Thus, according to our findings, one may speak of a certain tendency to an increased permeability

in organic psychoses, and a decreased one in schizophrenia Besides, it should be added that similar tendencies are equally marked in the other two psychotic reaction types, namely, in affective psychosis and in mental deficiency

Walter's bromide test has also been studied in epileptic patients Out of 87 cases, a distinctly increased permeability was found in only twelve (13.8 per cent) A moderate rise above the normal standard was observed, however, much more frequently, namely in 24 out of 87 cases (27.6 per cent) This obvious tendency to an increased permeability in epilepsy, presents an interest when confronted with the frequent observation of an increased permeability in organic diseases of the cerebrospinal system

In the light of the results obtained with the bromide test, which revealed a tendency to an abnormal permeability in various psychotic groups and in epilepsy, it seemed of interest to test by other procedures, the function of the barrier in the same diseases The question arose whether the abnormal

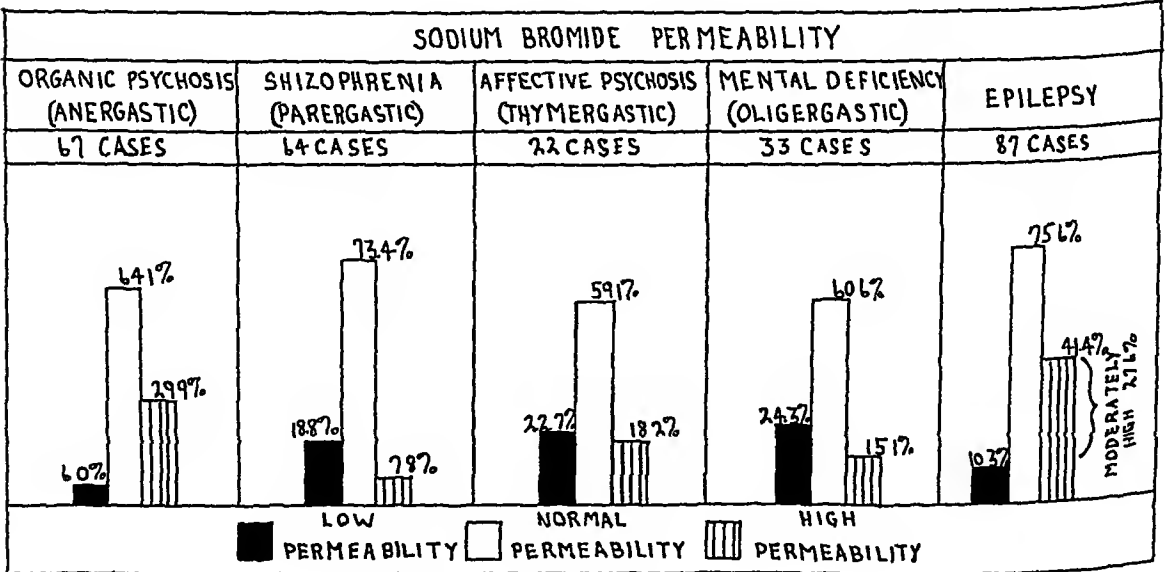


CHART I

behavior of the barrier is specific to bromide, or whether this behavior is conditioned by factors proper to the diseases, and may also be brought about by other methods. The problem of the distribution of calcium between blood and cerebrospinal fluid attracted my attention for the following reasons. The function of the vegetative system is assumed to be closely connected with calcium (Kraus, Zondek). On the other hand the vegetative system takes a conspicuous part in the modern literature on nervous and mental diseases. The calcium studies were carried out on one hundred and thirteen patients belonging to the four psychiatric reaction types mentioned above. Blood and cerebrospinal fluid were withdrawn at the same time for the determination of calcium in both blood and fluid. Considering, in accordance with other investigators, that the normal ratios, fluid-Ca/blood-Ca, expressed as percentage are to be found within 45 and 55, our results may be summarized as follows (Chart II)

1 Abnormal figures were found in

a small number of cases, namely in nine out of the 113 cases

2 In manic depressive patients and in mental deficiency cases the ratios are within normal limits

3 Increased ratios, fluid-Ca/blood-Ca, were observed in five out of forty-two cases of organic psychosis

4 In the schizophrenic group ratios below normal were found in four out of forty cases

These findings show that the distribution of calcium between blood and fluid cannot yield any help in the diagnosis of the diseases which were investigated. It is interesting to note, however, that the passage of calcium from blood into fluid follows the trend of bromide. It shows, as does the bromide test, that there is a tendency to an increased permeability in organic psychoses, and a low permeability in schizophrenia.

Our calcium studies have also been pursued in a series of 86 epileptic patients from the Springfield State Hospital. It may be mentioned in passing, that these studies, in addition to the

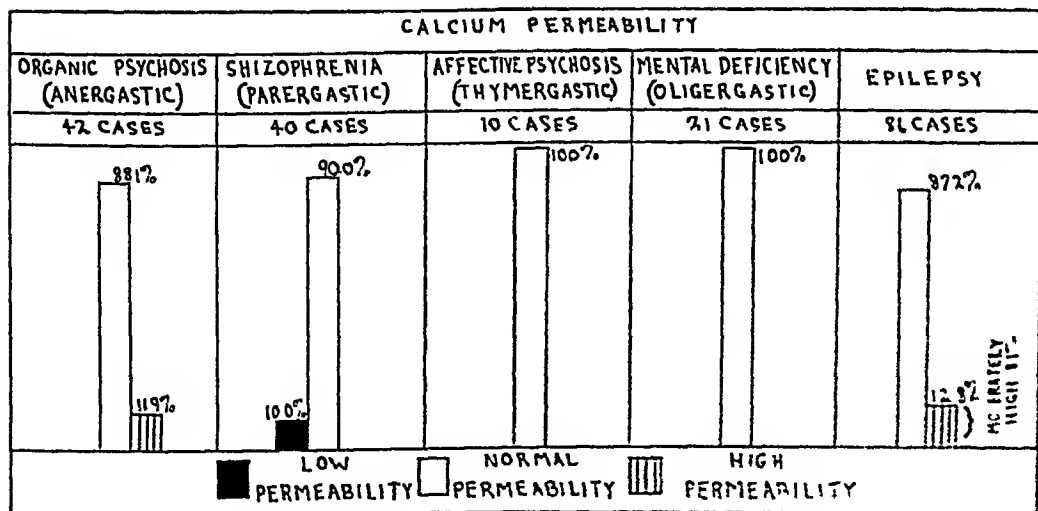


CHART II

mal limits in manic depressive patients² The results obtained in a study of 188 patients, carried out in the Phipps Clinic, in collaboration with the City Hospital, are somewhat different The graphic presentation of our findings shows the following essential features (Chart I)

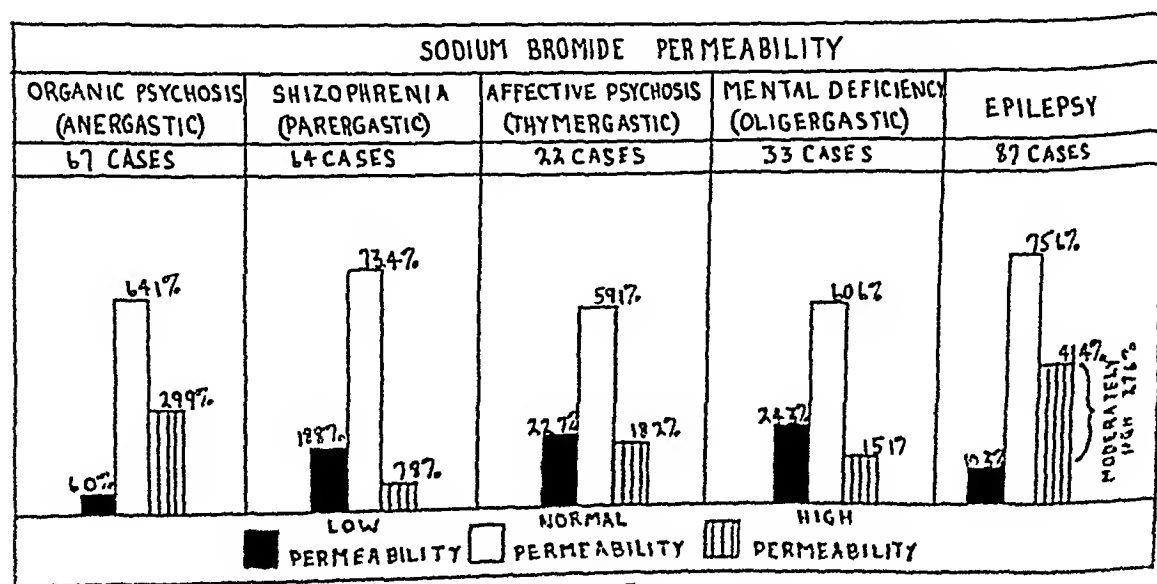
1 In each psychotic group the prevalent number of cases has a normal permeability It is worth noting that the percentage of normals is strikingly high in organic psychoses and in schizophrenia, that is, in the two psychotic groups in which, as mentioned above, an essentially abnormal permeability was found by most investigators

2 In our experience, however, an increased permeability was observed more frequently in organic psychoses, than in any other psychotic group; and a low permeability was found in a relatively high percentage of cases with schizophrenia, as compared to organic psychosis Thus, according to our findings, one may speak of a certain tendency to an increased permeability

in organic psychoses, and a decreased one in schizophrenia Besides, it should be added that similar tendencies are equally marked in the other two psychotic reaction types, namely, in affective psychosis and in mental deficiency.

Walter's bromide test has also been studied in epileptic patients Out of 87 cases, a distinctly increased permeability was found in only twelve (13.8 per cent) A moderate rise above the normal standard was observed, however, much more frequently, namely in 24 out of 87 cases (27.6 per cent) Thus obvious tendency to an increased permeability in epilepsy, presents an interest when confronted with the frequent observation of an increased permeability in organic diseases of the cerebrospinal system

In the light of the results obtained with the bromide test, which revealed a tendency to an abnormal permeability in various psychotic groups and in epilepsy, it seemed of interest to test by other procedures, the function of the barrier in the same diseases The question arose whether the abnormal



behavior of the barrier is specific to bromide, or whether this behavior is conditioned by factors proper to the diseases, and may also be brought about by other methods. The problem of the distribution of calcium between blood and cerebrospinal fluid attracted my attention for the following reasons. The function of the vegetative system is assumed to be closely connected with calcium (Kraus, Zondek). On the other hand the vegetative system takes a conspicuous part in the modern literature on nervous and mental diseases. The calcium studies were carried out on one hundred and thirteen patients belonging to the four psychiatric reaction types mentioned above. Blood and cerebrospinal fluid were withdrawn at the same time for the determination of calcium in both blood and fluid. Considering, in accordance with other investigators, that the normal ratios, fluid-Ca/blood-Ca, expressed as percentage are to be found within 45 and 55, our results may be summarized as follows (Chart II).

1 Abnormal figures were found in

a small number of cases, namely in nine out of the 113 cases.

2 In manic depressive patients and in mental deficiency cases the ratios are within normal limits.

3 Increased ratios, fluid-Ca/blood-Ca, were observed in five out of forty-two cases of organic psychosis.

4 In the schizophrenic group ratios below normal were found in four out of forty cases.

These findings show that the distribution of calcium between blood and fluid cannot yield any help in the diagnosis of the diseases which were investigated. It is interesting to note, however, that the passage of calcium from blood into fluid follows the trend of bromide. It shows, as does the bromide test, that there is a tendency to an increased permeability in organic psychoses, and a low permeability in schizophrenia.

Our calcium studies have also been pursued in a series of 86 epileptic patients from the Springfield State Hospital. It may be mentioned in passing, that these studies, in addition to the

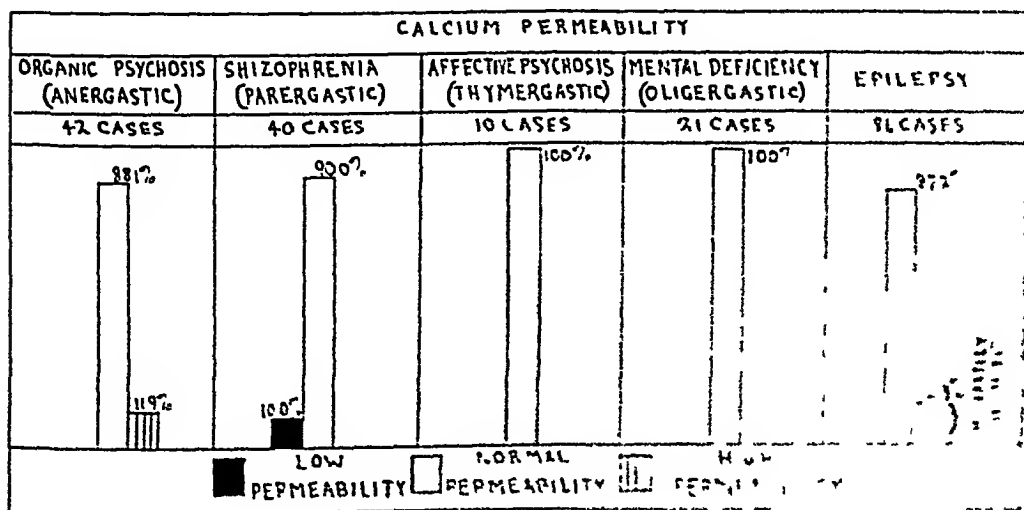


CHART II

problem of meningeal permeability, also contribute to the discussion of the assumed relationship between epilepsy and tetany. The ratios, fluid Ca/blood Ca, were found to be within the limits of 46 to 65, instead of within the normal figure of 45 to 55. Ratios slightly above the normal standards were found in seven cases, and distinctly above the normal in four cases. The high ratios in eleven out of 86 cases, and no cases with ratios below normal, suggest that there is a tendency in epilepsy to an increased permeability of the "barrier" to calcium, a tendency which appeared to be more accentuated when the bromide permeability test was used.

The therapeutic significance of the "meningeal permeability" lies in the fact, that it takes a prominent part in the theoretical considerations, aiming to justify certain therapeutic procedures, which have had a great vogue in the last few years. The endolumbar treatment should be mentioned first. In epidemic encephalitis, autoserum, serum of convalescents, specific vaccine of Levaditi, and casein have been used for endolumbar injections.⁸ It has also been claimed that tabetic pains, and delirium tremens have benefited by intraspinal injection of bromide.¹⁰ Finally, attempts have been made to treat schizophrenia with intrarachial injections of horse serum.¹¹ The theory of the intraspinal treatment is based on the following two conceptions. (1) The cerebrospinal fluid is the intermediary body through which the exchanges between the general circulation and the nervous system takes place. This view is derived from the experimental investigations showing

that, among various substances introduced into the general circulation, only those which could be detected in the cerebrospinal fluid, have also been found in the nervous tissue. These findings lead to the belief that the effect of a drug on the nervous system is conditioned by its presence in the cerebrospinal fluid. (2) The other conception has a bearing on the function of the barrier between blood and fluid. This function is, generally speaking, an interfering, or, to say the least, a selective one with regard to the passage into the fluid of substances introduced into the general circulation. Using the intraspinal way, one aims to insure the contact of the drugs with the nervous tissue.^{2, 12} One also assumes that the intraspinal treatment favors the passage of antibodies from blood into the cerebrospinal fluid, by the following mechanism. Any substance introduced into the spinal canal induces a more or less pronounced meningitis. On the other hand it has been shown by many investigators that congestion of the meninges, of whatever origin, is liable to increase the meningeal permeability toward blood constituents, and substances introduced into the general circulation.^{7, 8} With regard to the induced passage of antibodies from blood into fluid I refer, for illustration, to the following observations. The intraspinal administration of arsenobenzene and horse serum (Dujardin), in patients in whom the Wassermann reaction was negative in the fluid and positive in the blood, was followed by the commonly known meningeal reactions, and the Wassermann test became positive in the fluid. The inference is that the provoked meningitis increased the pas-

sage of luetic antibodies from blood into fluid¹³ Moreover, some data available in the literature are suggestive of a certain relationship between the effects of pyretotherapy and the barrier permeability Experimental studies have shown that in animals infected with various bacteria the permeability increases distinctly (L. Stern)¹⁴ An increased permeability has also been found to be induced by fever in schizophrenic patients (E. Storring)¹⁵ Finally, it has been demonstrated that the meningeal permeability in general paresis, being usually above the normal, experiences a further rise during the malarial treatment (E. Storring, A. Kral) In the light of these observations one may, plausibly, concede that the therapeutic effects in the diseases just mentioned, obtained with fever treatment in general and with the malaria therapy in particular, seem to be somewhat related to the induced functional changes of the barrier permeability

SUMMARY

1 The meningeal permeability, as tested by the distribution of bromide and calcium between blood and cerebrospinal fluid, shows a tendency to an increase in organic psychoses and epilepsy, and to a decrease in schizophrenia

2 The diffusible components of the cerebrospinal fluid should be estimated not as absolute values but as compared to the concentration of these components in the blood

3 The intraspinal treatment appears to be justified reasonably on the ground of the actual knowledge of the function of the barrier between blood and fluid

4 The increased permeability of the barrier, which was found to be induced by malaria therapy and fever treatment in general, may be considered as a contributing factor to the efficacy of these therapeutic methods

REFERENCES

- ¹STERN, L., and GAUTHIER, R. Les rapports entre le liquide céphalo rachidien et la circulation sanguine, *Arch Internat de Physiol*, 1921, **xxii**, 138-192
- ²KATZENFLOGEN, S. The physio-pathological significance of the meningeal permeability, *Am J Psychiat*, 1930, **xv**, 235-244
- ³KATZENFLOGEN, S. Experimental study on the sugar in blood and cerebrospinal fluid, *Jr Pharmacol and Exper Therap*, 1929, **xxxvi**, 231-234
- ⁴KATZENFLOGEN, S., and STÖLLER, M. La valeur sémiologique de la glyco-rachie. Étude critique, *Ann de med*, 1927, **xvii**, 460-472
- ⁵KATZENFLOGEN, S., and STÖLLER, M. Le rapport entre la glycémie et la glyco-rachie, sa valeur sémiologique. *Ann de med*, 1928, **xxiii**, 160-165
- ⁶MESTRAZAT, W. Le liquide céphalo rachidien normal et pathologique valeur clinique de l'examen clinique, 1912, A. Maloine, Paris
- ⁷KATZENFLOGEN, S. De l'augmentation de la perméabilité meningeale aux nitrates dans la meningite septique post-oculaire. *Schweiz med Wochenschr*, 1924, **xxviii**, 833-834
- ⁸ROCH, M., and KATZENFLOGEN, S. Traitement des formes exanthémateuses de l'encephalite épidémique par les injections intrarachidiennes de nitrates. *Schweiz med Wochenschr*, 1924, **xviii**, 835
- ⁹See bibliography of KATZENFLOGEN, S., and GOLDSCHMIDT, H. The permeability of the cerebrospinal fluid barrier. *Proceedings of the 12th International Congress*

Am Jr Psychiat, 1931, x (old series, lxxxvii), 1045-1055

¹⁰LIPPmann, H Zur endolumbalen Behandlung der lanzinierenden Schmerzen bei Tabes und spastischer Zustände an den unteren Extremitäten mit Bromnatrium, Deutsch med Wchnschr, 1923, xlix, 245-246

¹¹CARROLI, R S Aseptic meningitis in combating the dementia precox problem. New York Med Jr and Med Rec, 1923 cxviii, 407-411

¹²KATZENELBOGEN, S La symptomatologie de la méningite thérapeutique, Rev med de la Suisse Rom, 1928, xlviii, 967-975

¹³See bibliography in KATZENELBOGEN, S., ROGOVINE, S., and MONEDJIKOVA, V The relation between the Wassermann reactions in the blood and in the cerebrospinal fluid, contribution to the question of origin of antibodies, Arch Neurol. and Psychiat, 1929, xxi, 376-380

¹⁴STERN, L Les dernières recherches concernant le fonctionnement de la barrière hémato-encéphalique, Schweiz med Wchnschr, 1929, lix, 935-940

¹⁵STORRING, E Beiträge zum Permeabilitätsproblem, Arch f Psychiat, 1929, lxxxvi, 567-575

The Use of Histamin Hydrochloric Acid As a Test Meal*†

By HENRY H. HAFT, M.D., F.A.C.P., Syracuse, N.Y.

IN recent years there has been a revival of interest and a tendency to evaluate in their proper worth, the various test meals that have been used to determine gastric secretion. Briefly, the Ewald test meal with coffee, tea and toast, seven per cent alcohol, the Schmidt test meal containing meat, bread and vegetables, the raisin and rice evening meal,—all have been given careful scrutiny. The consensus of opinion seems to be that any one test if standardized by one man or in one clinic will give the desired information sought by the investigator.

In functional anacidity, in chronic gastritis with excess mucus production, in heterochylia and true achylia the above mentioned tests are not satisfactory.

In 1923, Ivey, McIlwain and Jarvis applied a one per cent solution of histamin hydrochloric acid to Pavlov pouches in dogs with a resulting prompt and decided secretion of gastric juice. Matheson, in England, and Carnot injected subcutaneously histamin hydrochloric acid and a like effect was shown.

*Read before the Alumni of Syracuse Medical College at the University Hospital May 20, 1931.

†Received for publication, July 13, 1931.

Recently, Gilman and Cowgill of Yale University have proved fairly definitely that histamin acts specifically on the acid-secreting glands and its chief effect seems to be to stimulate production of hydrochloric acid if these glands are functioning. The rapid increase in pepsin following the injection of histamin is not as a result of the direct stimulating effect of the pepsin-secreting glands but rather is due to a generalized flushing of the gastric mucosa and thus the pepsin is increased in a somewhat mechanical fashion. Histamin has no direct stimulating action on the pepsin-secreting glands.

Histamin is a product formed by the putrefactive action of bacteria on the amino-acid histidine. When injected in quantities of one milligram or over it is accompanied by such systemic reactions as fall of blood pressure, increase in pulse rate, flushing of the face, and throbbing sensation in the head with accompanying slight headache. In a dose of one-third of a milligram, this preparation showed absence of these systemic reactions while its effect on gastric secretion remained most pronounced. In this dose the parietal or oxyntic cells of the gastric mucosa are stimulated to secrete hydrochloric acid in a free state and some

of these shock phenomena of histamin are noted

Here, then, is a valuable agent to tell us whether we are dealing with a true or false gastric anacidity. If the parietal cells are functioning, hydrochloric acid will be secreted under the stimulus of this agent. Further, it will be free from the food used as the test meal and it will give more nearly true acid values.

Histamin hydrochloric acid is not a stimulus to the gastric enzyme, pepsin.

For the last year and a half, I have been using histamin hydrochloric acid (Amido-Roche), in all cases coming to the University Hospital, in which we were interested in gastric secretion. This included cases not particularly gastric in their nature, such as chronic eczema, colitis, poisoning due to heavy metals, kidney disturbances and other metabolic diseases. More than 150 such cases have been studied up to date, so that we feel we are able to draw certain conclusions from the test as used in our hands.

Among the contraindications to the test, we have included pregnancy, because of the possible action of histamin in stimulating uterine muscle contraction, and hyperthyroidism, because of a possible effect in producing vasomotor instability.

We have learned that a very safe and harmless dose is one-third to one-fourth milligram. In a few cases one-half milligram of histamin has been used with no untoward effect. We have found that in the smaller dosage it has the same diagnostic value as in the larger dosage.

In most of our cases careful observations were made of the effect on

the pulse rate, blood pressure and other general systemic reactions following its use and much to our surprise and gratification, no unfavorable effects were noted. Usually the blood pressure remained at a fixed level and the pulse rate became even slower 15 minutes to one-half hour after the injection of histamin. In only three cases were flushing of the face and some uncomfortable sensations in the head noted.

Briefly, we performed the test as follows.—On a fasting stomach the duodenal tube is passed into the stomach. This is the usual perforated metal-tip bucket with a thin rubber attached. An estimation is made of the pulse rate and blood pressure and extraction of the gastric content is accomplished. Then histamin hydrochloric acid is injected and every fifteen minutes an extraction is made and labeled, either 1, 2, 3, or 4, depending upon the time of the extraction. With these subsequent extractions, pulse rate and blood pressure were obtained and noted.

In the differentiation between true and false achylas, the test is of inestimable value. In the true achylas, such as we find in pernicious anemia and a few cases of gastric carcinoma, no free acid was found after fractional extraction carried on for a two hour period with fifteen minute intervals. In many cases that had been characterized as true achylas following the common Ewald test meal, free acid was obtained either in the first fifteen minute extraction after the histamin or in the second or third subsequent extraction. In gastric ulcer and duodenal ulcer, the response to

histamin is characterized by a rapid and maintained high acid curve which differs somewhat from the curve described by Rehfuess and others. In chronic gallbladder disease and allied conditions, in which we have been in the habit of obtaining low acid figures and sometimes achylas, in most of our tests, free acid in fairly normal concentration was obtained.

I believe that I am justified in making the following conclusions as to the use of this method:

1 In differentiating between false and true achylia, it is one of the best

methods to use. Further, it is practical and safe.

2 It may stimulate sluggish and dormant gastric secretion.

3 It can be used as a means of determining the amount of hydrochloric acid secretion.

4 It is a powerful stimulant to the parietal or acid-secreting cells of the stomach.

I want to express my appreciation to the members of the Staff for the co-operation in this study and for the privilege of following out this line of investigation, through the courtesy of Dr. E. C. Reifenshein.

San Francisco as a Medical Center

By WM J KERR, M D , F A C P , *San Francisco, California*

Our visitors to the San Francisco session will find a cosmopolitan city, young in point of years but already rich in tradition, modern in external appearance but retaining the charm of earlier days. Marks of the period of Spanish occupation are still evident in its family and place names, in its Mission, which was founded in 1776; and in some of its most cherished customs. Among its population are large racial groups who have brought their culture from many European and Asiatic countries and have retained their individuality to influence the life and thought of this community.

Attracted by the early reports of a warm and equable climate and a wide expanse of rich soil, the early settlers came. These were soon followed by that vast horde, the Argonauts, lured by the cry of "Gold! Gold!", who began one of the greatest pilgrimages the world has ever known. Most of those who came in quest of easy riches from the miner's pan and cradle were disillusioned and soon turned to the soil, the woods and the sea as sources of livelihood. San Francisco became the center of commerce and shipping in the West. With the great influx of adventurers and home-seekers came a number of well-educated men and women and among them a few physicians who had been well trained in the

famous schools on the eastern seaboard and abroad. They transplanted the best scientific and practical medical teaching of the day to a locality where it could flourish unhampered by outworn traditions, and, from the blending arose a new center of medical thought and practice at the Golden Gate.

The rapid growth of San Francisco during the "Gold Rush" days introduced the problem of conserving the health of its people. Many of those who came soon exhausted their resources. In 1850, when the population of San Francisco was less than 100,000, a city hospital became a necessity to care for the indigent sick. Previous to this time such public charges were treated on a contract basis. The care of the destitute sick must have become an acute problem, for, in 1851, the French Mutual Benevolent Society was founded and the German General Benevolent Society was projected. The number of benevolent societies organized by special groups of the citizens increased so that, by 1871, eighty societies classed as benevolent had been formed. The San Francisco Medical Benevolent Society, founded in 1870, later became the California Academy of Medicine. The founders stated that "the objects of this society are for the protection and relief of

deserving physicians and their families who may suffer from sickness and want and to promote kindly professional and social intercourse among themselves and the profession at large" In recent years the Academy of Medicine has limited its objectives Several meetings have been held each year, and men from all parts of the world have addressed the members and guests upon medical topics of a scientific and practical nature

By 1870 the San Francisco County Medical Society had become an active force in the professional life of the city The Society purchased its own home in 1926 (figure 1), where frequent general and section meetings are held A reference library of approxi-

mately 13,000 volumes is available for its members Other medical societies have been established until now there is no want for opportunity to attend frequent gatherings each month

With the growth of San Francisco and the West, the pioneers in medicine recognized the need for some center of medical education near at hand With such a purpose in mind, a small group under the leadership of Dr H H Toland founded the Toland Medical College in 1864, and delivered the first regular course of medical lectures in the state Among this small group were Dr L C Lane and Dr Henry Gibbons who later joined with others to form the Cooper Medical College under the direction

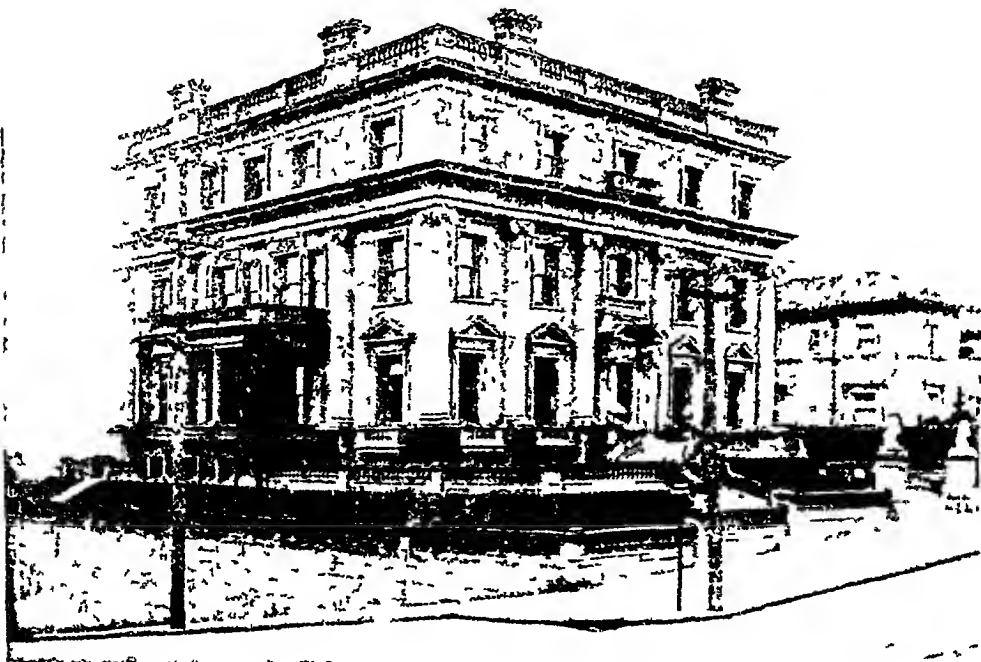


Fig 1 Home of the San Francisco County Medical Society

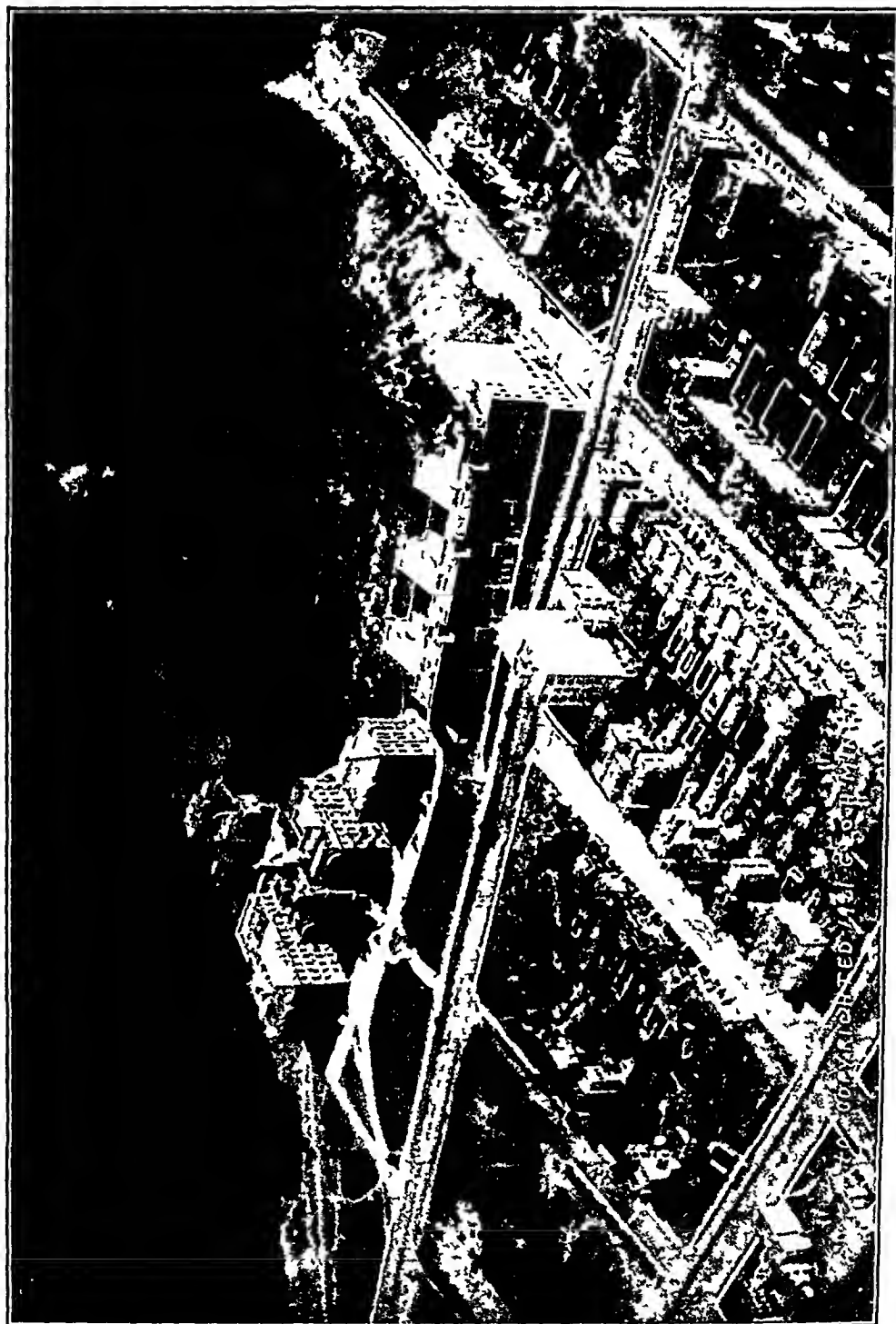


Fig 2 Birdseye View of the University of California Medical School Campus, San Francisco.

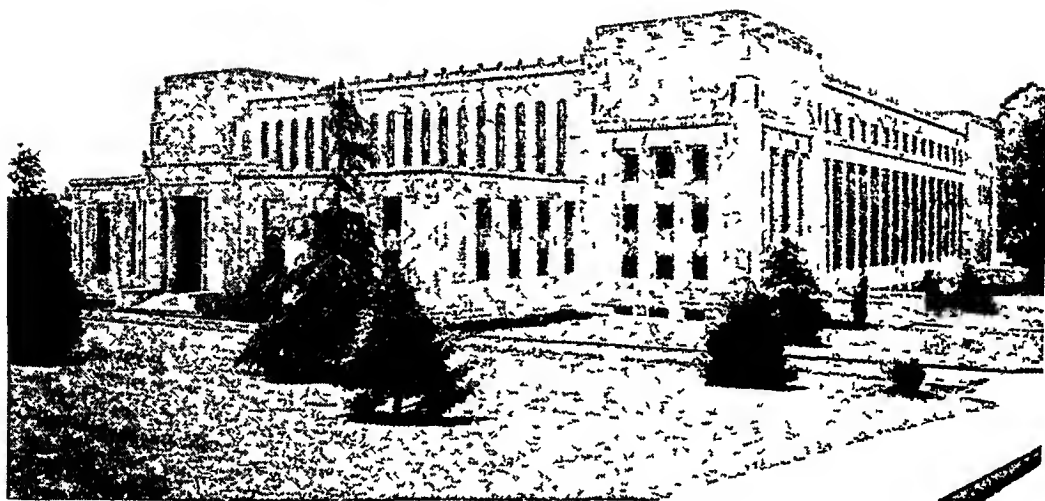


Fig 3 Life Sciences Building, Berkeley, California

of Doctor Lane. This college later became the Medical Department of Leland Stanford Jr University. The original Toland Medical College, located near the center of the growing city, was reorganized in 1870, and to its faculty came the illustrious John LeConte as Professor of Physiology, who, with his brother, Joseph LeConte, were outstanding figures in the growing University of California (founded in 1868). Dr. R. Beverly Cole joined the faculty as Professor of Obstetrics and Gynecology, and Dean, in 1870, and promoted an affiliation with the University of California which was completed in 1872. Among the notable members of this new faculty were Dr. H. H. Toland, the Drs. H. Gibbons, Senior and Junior, and Dr. A. Barkan. Under the deanship of Dr. R. Beverly Cole, the University of California Medical School raised its standards for admission, and established a four-year curriculum of

instruction. In 1898 the state of California provided funds for new buildings to house the medical school which were erected on Parnassus Heights (figure 2), commanding a superb view of the city and its environs, on land generously donated by the late Adolph Sutro. At the time of the earthquake and fire in 1906, the first two years of instruction were transferred to the University at Berkeley and the medical school building was converted into a hospital and outpatient building for clinical instruction.

Among the notable members of the clinical faculty during this period were Doctor Cole, Dr. T. L. Huntington, Dr. Harry Sherman, Dr. Wm. Watt Kerr, Dr. Douglas W. Montgomery, Dr. Chas. von Hoffman and Dr. Wm. B. Lewitt. The great Jacques Loeb was Professor of Physiology.

In 1912 the faculty was reorganized with Dr. Herbert C. Moffitt as Dean.

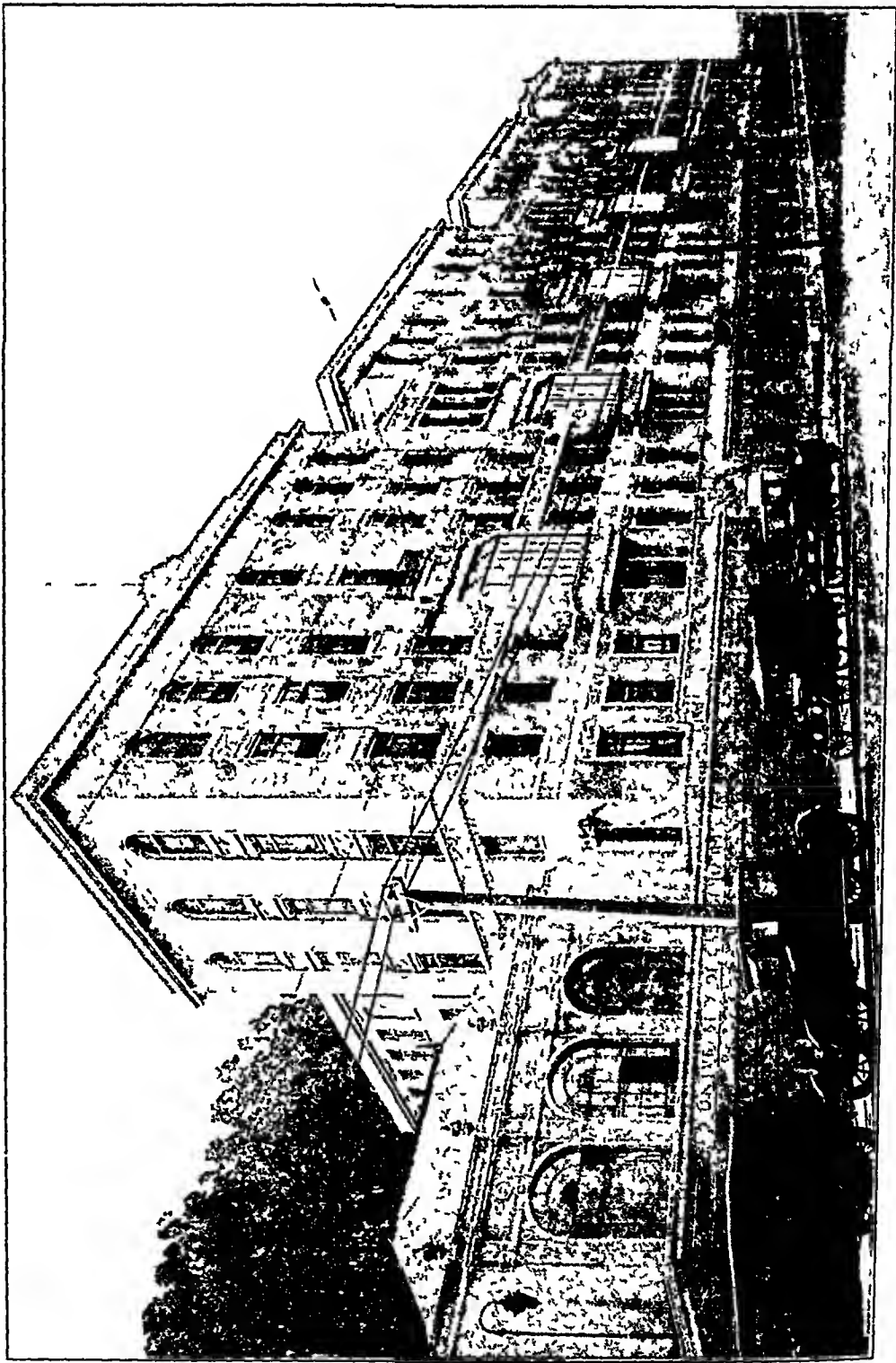


Fig 4 University of California Hospital

under whose leadership the medical school continued to grow in importance as a center of medical education. Dr W I Terry became Professor of Surgery and Dr Howard Morrow, Professor of Dermatology. The clinical departments of Obstetrics and Gynecology and Pediatrics were placed on a full-time basis under Dr Frank W Lynch and Dr Wm Palmer Lucas respectively. Many additions were made to the preclinical staff, Dr Frederick P Gay became Professor of Pathology and Bacteriology, Dr Herbert M Evans, Professor of Anatomy, and Dr Walter R Bloor, Professor of Biochemistry. In 1915, the Hahnemann Medical College of the Pacific was taken over, and since

that time elective courses have been offered in Homeopathy. In the past few years the departments of Medicine and Surgery have been developed on a full-time basis. In 1928, Dr Langley Porter became Dean of the Medical School, devoting full time to the post.

In 1931 the state legislature appropriated the sum of \$600,000 for a new clinic building. An increasing number of gifts from friends of the medical school have made it possible to increase the educational and research facilities in all major departments.

In 1917 the University of California Hospital was built on the Parnassus site from funds donated by private

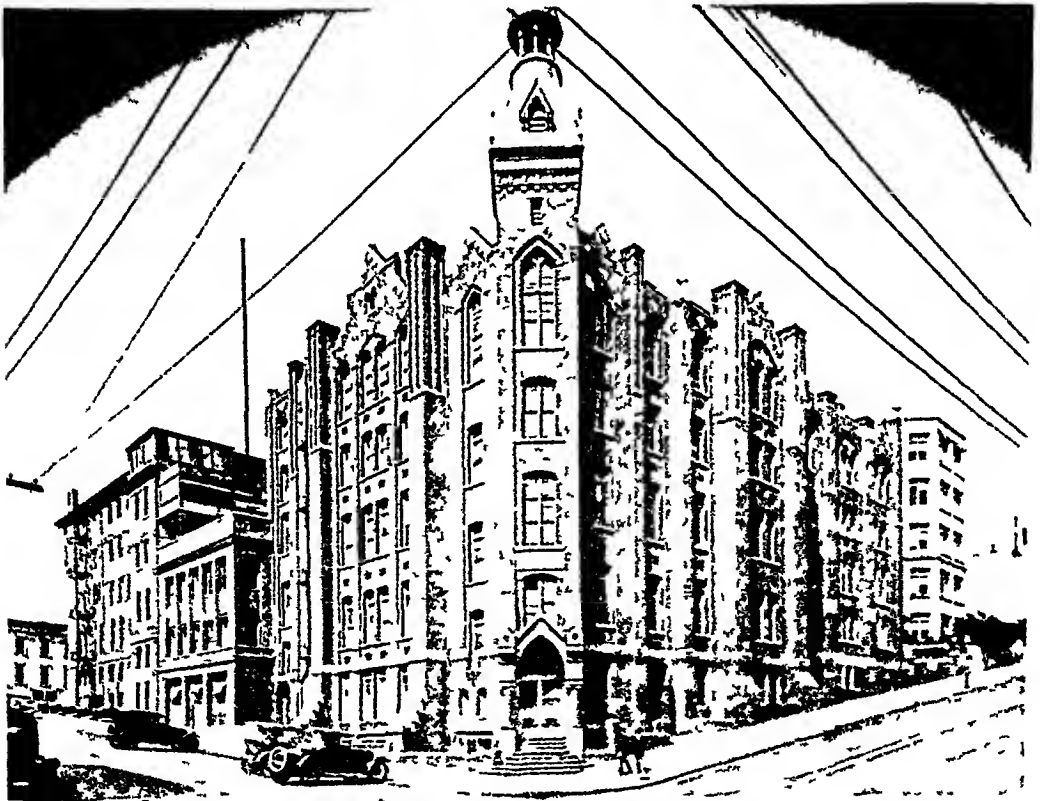


Fig 5 Stanford University Hospital

subscription to the University. Since 1928 the instruction of the last three years has been given in San Francisco. The departments of Anatomy, Physiology and Biochemistry are housed in the new Life Sciences Building (figure 3), completed in 1930, on the University Campus in Berkeley.

Clinical instruction in the University of California Medical School is given at the University of California Hospital (figure 4), in the San Francisco Hospital and at the Children's Hospital, which is an affiliated institution. A fifth or intern year in an approved general hospital is required for graduation, and many hospitals in the state cooperate to provide satisfactory practical experience. By spe-

cial arrangement, the fifth year may be spent in research.

The University of California Hospital is a teaching hospital of 287 beds with a limited number of private rooms for the convenience of members of the staff. The number of students in each class is limited to 60, and men and women of senior standing are admitted on equal terms. Certain courses in chemistry, physics, biology, English and a foreign language are required for admission.

The University of California Medical School has an admirable reference library on the San Francisco campus and a special library for the pre-clinical branches in the Life Sciences Building in Berkeley. A packet service

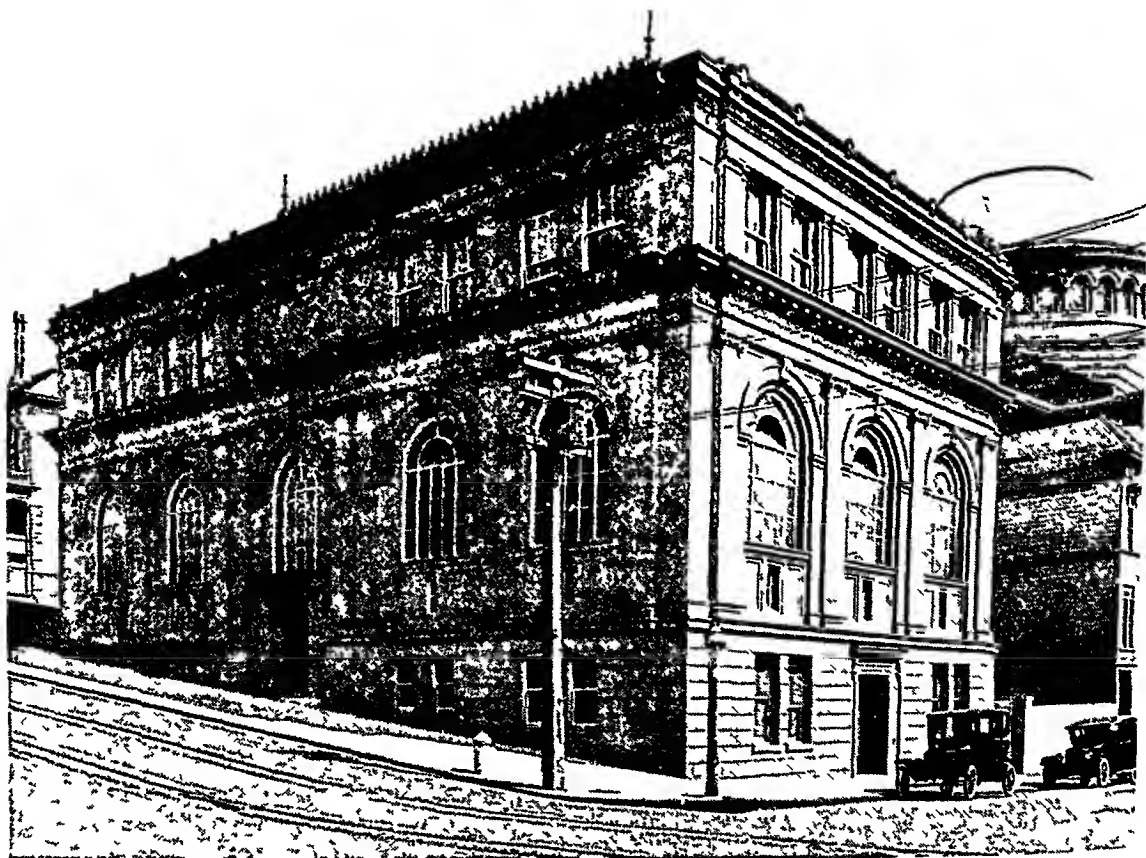


Fig 6 Lane Medical Library

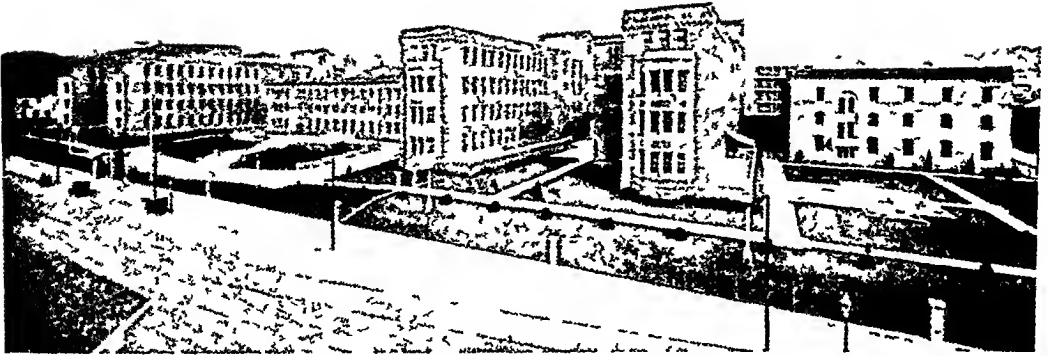


Fig 7 San Francisco Hospital

to physicians throughout the state has been an important development

The Hooper Foundation for Medical Research is located on Parnassus Heights in a building adjacent to the University of California Medical School and Hospital, with which its work is closely correlated. This institution was established in 1913 through the generosity of Mrs. Hooper in memory of her husband, George Williams Hooper as an institute for medical research. From the beginning, the Hooper Foundation became a center of research activity. Under the direction of Dr. George H. Whipple, important contributions were made in the field of pathological physiology and in tropical medicine. It was in this laboratory that Doctor Whipple and his associates first demonstrated the value of liver in treating experimental anemia. In recent years Dr. E. L. Walker has made contributions to the field of infection and immunity through studies in tuberculosis and leprosy and through studies on chemotherapy. Under the direction of Dr. Karl F. Meyer, studies of benefit to

the state and nation, have been made on botulism, epidemic poliomyelitis, undulant fever, tularemia and poisoning by shellfish. The Pacific Institute of Tropical Medicine, under the direction of Dr. A. C. Reed, is closely affiliated with the Hooper Foundation and the Medical School.

The Stanford Medical School was established in 1908 under an agreement with Dr. Levi Cooper Lane who transferred the properties and equipment of the Cooper Medical College to the Leland Stanford Jr. University. Dr. Elias Samuel Cooper, the uncle of Dr. Lane, had conducted a college under the name of the Medical Department of the University of the Pacific from 1858 to 1864, when it was discontinued. This medical college was reorganized in 1870 and, in 1872, was affiliated with the University College under the name of the Medical College of the Pacific. In 1882 the latter was succeeded by the Cooper Medical College, incorporated by Dr. Levi Cooper Lane. The first building of the medical group was built by Dr. Lane in 1882 on land donated by himself for

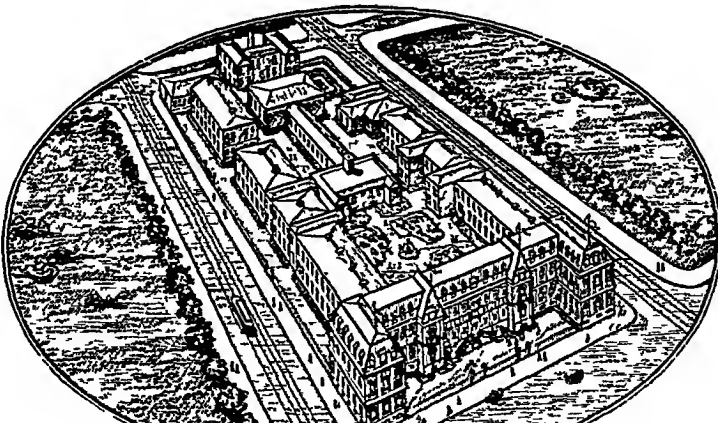


Fig 8 Infirmary, Laguna Honda Home

the purpose. An addition to the original building was given by Dr Lane in 1890. Dr Lane built the Lane Hospital in 1894, endowed the Lane Medical Lectureship in 1896, and made provision for a library building. Endowment funds were provided by friends of the College.

The Stanford University Hospital of 130 beds (figure 5) was built in 1917. The Lane Medical Library (figure 6), founded by the Directors

of the Cooper Medical College as directed by the will of Mrs. Levi Cooper Lane, contains 73,500 volumes and is one of the most complete medical libraries in America. The building was constructed in 1912. Many friends have contributed funds to provide historical collections in special fields, and among its most generous friends has been Dr. Adolph Barkan. The medical profession of the San Francisco Bay region and throughout the state



of California has been greatly assisted by having such a complete reference library near at hand

The early faculty of the Cooper Medical College included such outstanding teachers as Dr Levi Cooper Lane, Drs H Gibbons, Senior and Junior, and Dr Adolph Barkan. Later Dr Hans Zinsser became Professor of Bacteriology and Immunity. For a number of years Dr Ray Lyman Wilbur was Professor of Medicine and Dean before assuming the presidency of the University. Dr Stanley Stillman, Dr Emmet Rixford

and Dr Adolph Barkan held important faculty positions. Dr Albion Walter Hewlett, who was Professor of Medicine until his untimely death, was an inspiring teacher and investigator. Dr Wm Ophuls who came to San Francisco as Professor of Pathology and Bacteriology in 1898, has held an honored position in the scientific life of the school and community, and in recent years has been Dean of the medical school. Dr Thomas Addis has made valuable contributions to the field of pathological physiology.

Instruction in Anatomy, Bacteriolo-



Fig 10 Franklin Hospital

gy, Biochemistry, Histology, Neurology and Physiology is given on the campus at Stanford University. The entering class is limited to 50 students who have completed three full years of academic studies, with required courses in chemistry, physics, biology and English, and who have a reading knowledge of French or German.

The work of approximately the last three years is offered at the Stanford University School of Medicine in San Francisco. Clinical facilities are available for 50 students at the Lane Hospital with approximately 150 teaching beds and on the Stanford Service at the San Francisco Hospital. A large outpatient department is located adjacent to the Lane and Stanford Hospitals. The Hydrotherapeutic and X-Ray Departments and the Clinical Laboratories are located in the Stanford University Hospital, which has a capacity of 130 beds. A fifth or intern year in an accredited hospital or in special laboratory work is required of all students before graduation.

In addition to the two university hospitals there are many others which, from the early days of San Francisco,

have developed as expressions of the desire for service which characterizes the public and our profession alike. The total number of available hospital beds in San Francisco is beyond the needs of its people. In the Marine and Letterman General Hospitals there are many beds for special government groups, and in the Southern Pacific Hospital for employees who are sent from other states in the West. Many patients from outside the city also seek professional care in the city.

It is beyond the scope of this paper to discuss the hospitals and medical facilities of the entire region. The counties bordering on the San Francisco Bay are, however, closely united in upholding the best traditions of medicine. In Alameda County there are many outstanding hospitals, among which may be mentioned the Highland Hospital, operated as a general hospital and modern in every respect, and the Ernest V. Cowell Memorial Hospital which serves as the health center for students of the University of California. San Mateo County, lying south of San Francisco, on the peninsula, boasts one of the finest

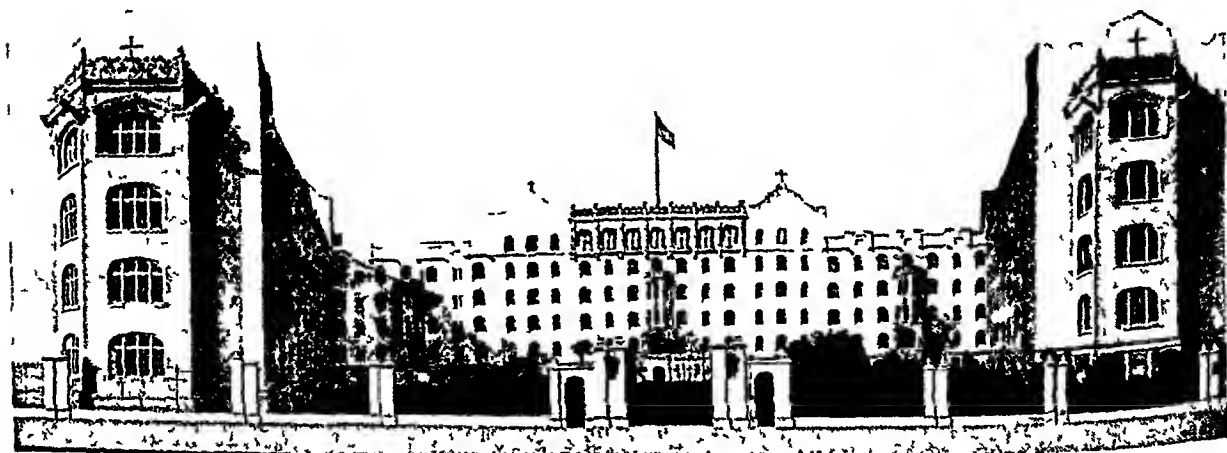


Fig 11 St Mary's Hospital

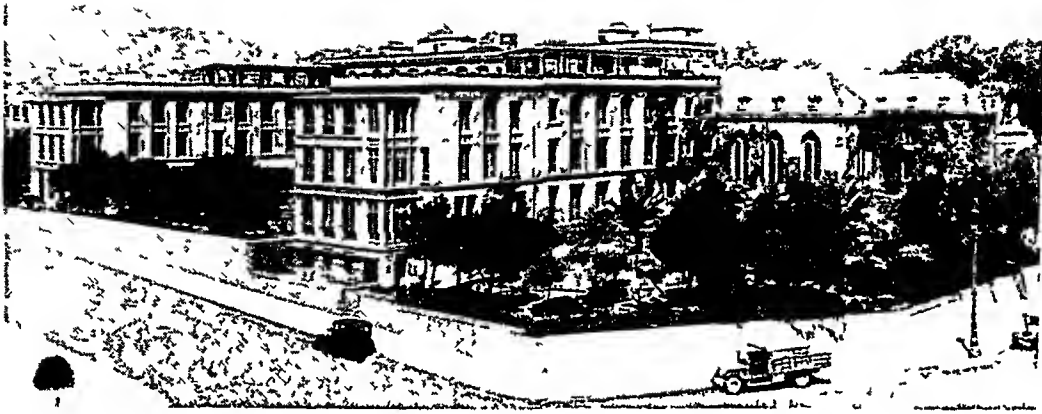


Fig 12 St Luke's Hospital

hospitals of moderate size in America. It was built and endowed by the late Mrs. Whitelaw Reid as an outgrowth of interest in Red Cross work during the World War. The new Palo Alto Hospital has just been completed in Palo Alto to serve the needs of the community and under a special arrangement is available for students of Stanford University. This hospital is on university property and is under the supervision of the Director of the Lane and Stanford Hospitals.

The San Francisco Hospital (figure 7), one of the most modern general or municipal hospitals in America, was begun in 1909 and the main group of buildings was completed in 1915. The total cost of construction and equipment was approximately \$3,500,000. Accommodation was provided for 512 patients. With additions, since 1915 and including new wards the capacity has been increased to 1280 beds. There are special departments for

tuberculosis and contagious diseases. Land has recently been purchased, upon which will be constructed a new Psychopathic Institute of 149 beds and a Cancer Institute of 198 beds. The hospital is under the administrative control of the municipal Department of Health and is supported by taxation. From the early days in San Francisco the city has made ample provision to care for its sick, and this modern group is but the last of a long list of structures built for the purpose. The professional services of San Francisco Hospital are divided equally between the clinical staffs of the two university medical schools. The spirit of cooperation between the municipal authorities and the medical schools has been most cordial, and the highest type of instruction has been given to students under this arrangement.

The Laguna Honda Home (figure 8) is in part a hospital for chronic

diseases and in part an institution for the indigent and infirm of the city and county of San Francisco. There are 500 beds for patients, and living accommodations for 2000 of the indigent and infirm. The staffs of the two medical schools render the professional service, and patients are available for instruction in the chronic disorders and diseases of the aged. The city of San Francisco also maintains an official emergency service with stations in several sections of the city. A pre-

ventorium for tuberculosis is maintained in Redwood City approximately 25 miles south of San Francisco.

The San Francisco Health Department is under the direction of a full-time and efficient administrator who is concerned with the promotion of general health and the control of communicable diseases. The city ranks high among American cities in its health rating.

The French Hospital (figure 9) is owned and operated by a French Mu-



Fig 13 Entrance to Main Building, Children's Hospital

tual Benevolent Society which had its origin in 1851, when the need arose to provide some care for the poor and destitute French who came to California in quest of gold. At present the Society has a membership of 9,000 restricted to French people or people of French extraction and those speaking French, and strives to give the best care and treatment to its members. The Society owns and operates the French Hospital of 220 beds, which is modern and complete in all respects. The professional staff includes many outstanding physicians and surgeons of French extraction.

The present Franklin Hospital, formerly the German Hospital, (figure 10) was completed in 1908 and is the third hospital building owned by the German Benevolent Society. The Society was founded in 1854, and the first hospital to provide care for its members was built in 1857. The present modern and well-equipped hos-

pital occupies a sheltered site near the center of the city.

The first Marine Hospital in San Francisco was opened in 1853. Previous to this time seamen were given medical relief by contract surgeons. For two years previous to 1853, seamen were treated on board a revenue bark stationed off Fort Mason. A second Marine Hospital was constructed, in 1874, on the site of the present hospital and was in continuous operation until 1931. The new Marine Hospital has 400 beds and is complete in every detail. Outpatient departments are conducted at the hospital and in the Appraisers' Building near the water front. This hospital provides care and treatment for sick and disabled seamen of the American Merchant Marine. Service is also rendered to employees of the Government injured in line of duty and to beneficiaries of the Employees' Compensation Commission, to officers and en-

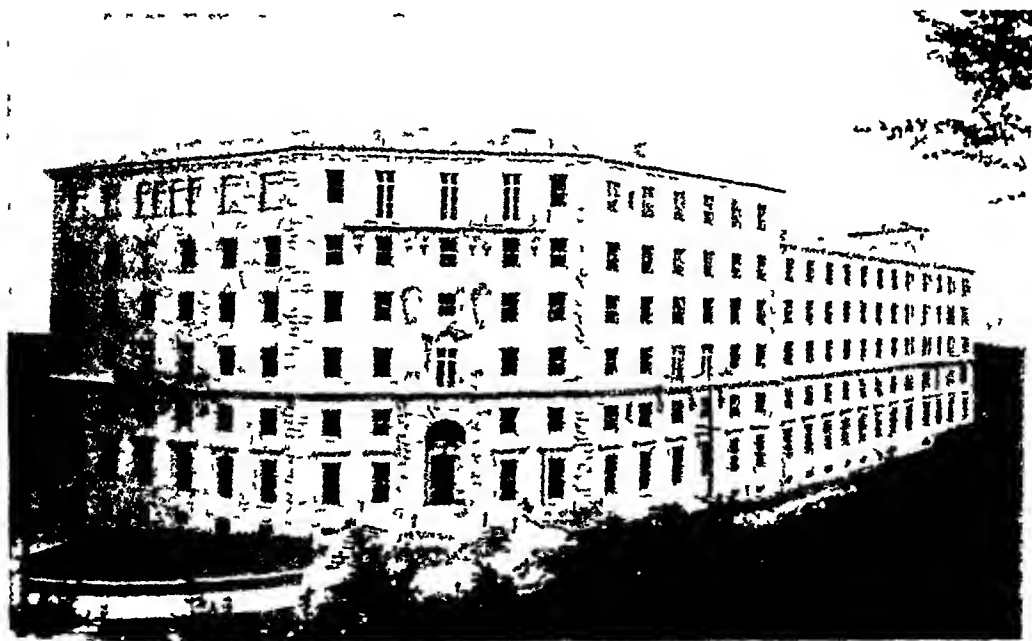


Fig. 14 St. Joseph's Hospital

diseases and in part an institution for the indigent and infirm of the city and county of San Francisco. There are 500 beds for patients; and living accommodations for 2000 of the indigent and infirm. The staffs of the two medical schools render the professional service, and patients are available for instruction in the chronic disorders and diseases of the aged. The city of San Francisco also maintains an official emergency service with stations in several sections of the city. A pie-

ventorium for tuberculosis is maintained in Redwood City approximately 25 miles south of San Francisco.

The San Francisco Health Department is under the direction of a full-time and efficient administrator who is concerned with the promotion of general health and the control of communicable diseases. The city ranks high among American cities in its health rating.

The French Hospital (figure 9) is owned and operated by a French Mu-



Fig 13 Entrance to Main Building, Children's Hospital

tual Benevolent Society which had its origin in 1851, when the need arose to provide some care for the poor and destitute French who came to California in quest of gold. At present the Society has a membership of 9,000 restricted to French people or people of French extraction and those speaking French, and strives to give the best care and treatment to its members. The Society owns and operates the French Hospital of 220 beds, which is modern and complete in all respects. The professional staff includes many outstanding physicians and surgeons of French extraction.

The present Franklin Hospital, formerly the German Hospital, (figure 10) was completed in 1908 and is the third hospital building owned by the German Benevolent Society. The Society was founded in 1854, and the first hospital to provide care for its members was built in 1857. The present modern and well-equipped hos-

pital occupies a sheltered site near the center of the city.

The first Marine Hospital in San Francisco was opened in 1853. Previous to this time seamen were given medical relief by contract surgeons. For two years previous to 1853, seamen were treated on board a revenue bark stationed off Fort Mason. A second Marine Hospital was constructed, in 1874, on the site of the present hospital and was in continuous operation until 1931. The new Marine Hospital has 400 beds and is complete in every detail. Outpatient departments are conducted at the hospital and in the Appraisers' Building near the water front. This hospital provides care and treatment for sick and disabled seamen of the American Merchant Marine. Service is also rendered to employees of the Government injured in line of duty and to beneficiaries of the Employees' Compensation Commission, to officers and en-

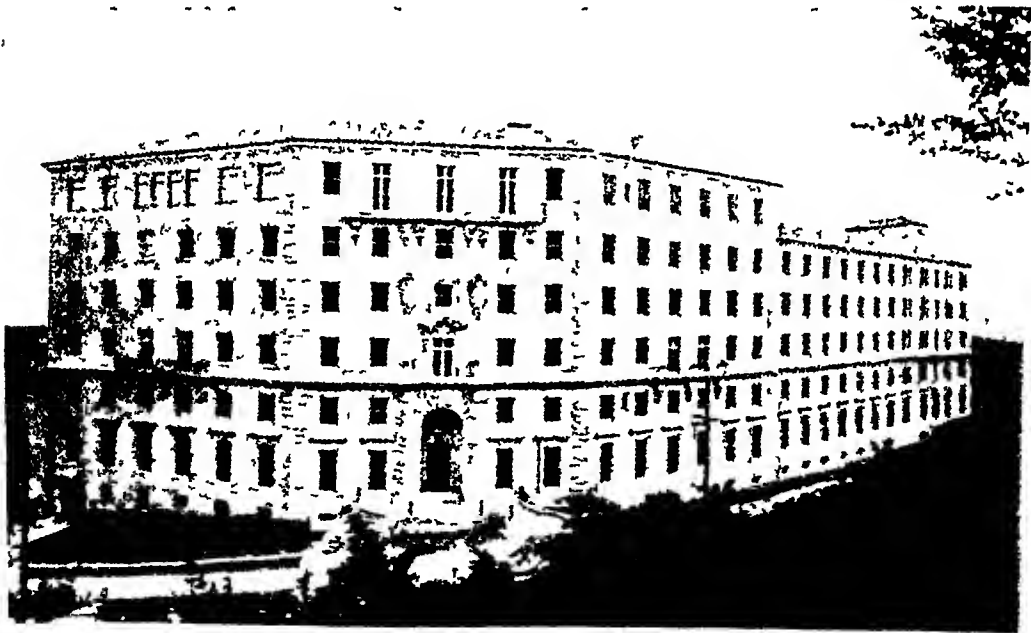


Fig. 14 St. Joseph's Hospital

listed men of the U S Coast Guard, Coast and Geodetic Survey, Light-house Service, and to seamen of the Bureau of Fisheries and of Army transports. Marine Hospitals also admit sick immigrants for treatment.

The St. Mary's Hospital (figure 11), the oldest Catholic Hospital in California, was opened in 1857 by the Sisters of Mercy. A new and larger hospital was constructed on Rincon Hill in 1861. This building, with additions, was destroyed by the earthquake and fire in 1906, but at once a new site was selected near Golden Gate Park and within five years a modern hospital was constructed. Additions were made in 1926, bringing the capacity to 325 beds. This hospital has held an important place in the community.

The St. Luke's Hospital (figure 12) was established in 1871, by the Rev. Thomas Woodley Brotherton,

M.D., D.D., who practiced medicine in the mining section of the state until 1855 and who, in 1860, was ordained a Deacon in the Episcopal Church. The original building with additions was destroyed in 1906. In 1911, the present buildings were erected by Lydia Paige Montague, Ogden Mills and Elizabeth Mills Reid, in memory of Calvin Paige and Darius Ogden Mills. Additions, in 1924, increased the capacity to 200 beds. This hospital aims to meet the demand for so-called "middle-class" hospital care by offering moderate rates to those who pay full costs, and by supplementing the income from those who can pay but part of the costs, through the agency of endowment funds.

The Hospital for Children and Training School for Nurses, commonly known as the Children's Hospital (figure 13) was founded in 1875. Although primarily a benevolent institu-

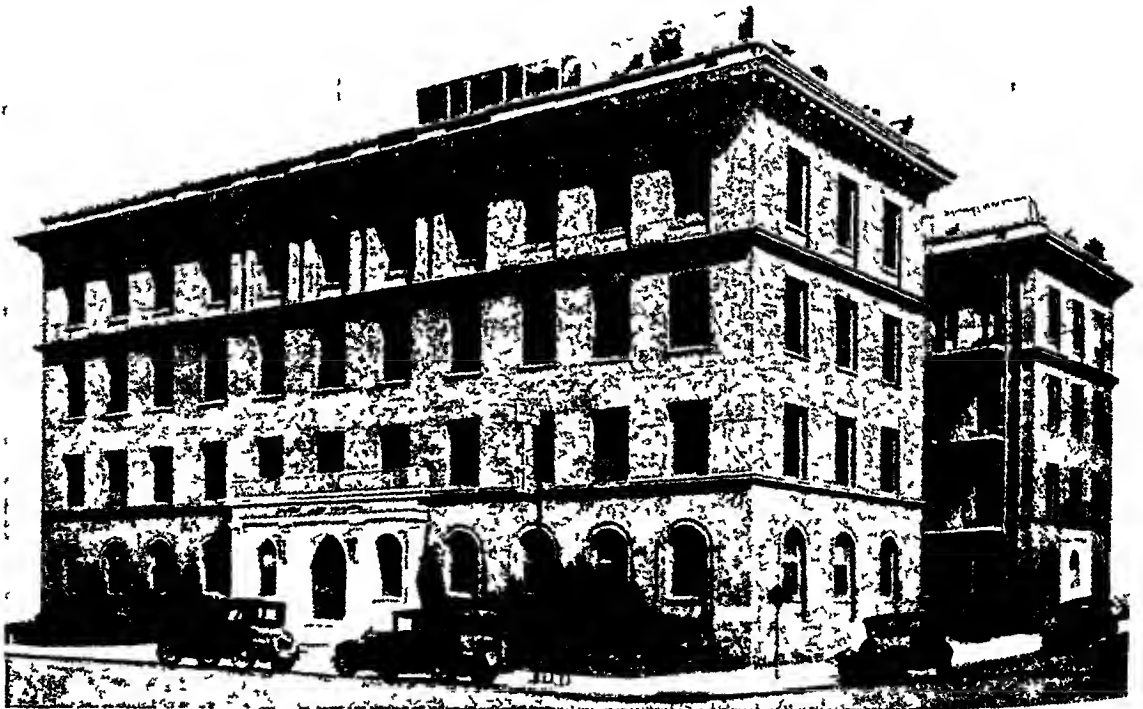


Fig 15 Mount Zion Hospital

tion, both private and service patients are accommodated. The present capacity is 275 beds, with an outpatient department. One wing is devoted entirely to the care of communicable diseases, and another wing provides excellent maternity care. Women patients with general medical and surgical conditions are cared for in the main building and there are special wards for children.

The St Joseph's Hospital (figure 14), operated by the Franciscan Sisters of the Sacred Heart, was erected in 1892. Additions were made in 1900 and in 1906. Since 1906 this institution has been known as St Joseph's Home and Hospital, providing service to the incurable and admitting to the hospital medical and surgical patients.

In 1928, a new modern hospital building was completed on the site, and is operated as a religious and charitable institution.

The Mount Zion Hospital (figure 15) is a general hospital of 150 beds operated by the Federated Jewish Charities of San Francisco. The first hospital was opened in 1897 but was so inadequate that two years later a larger structure was provided which served until 1912, when a modern hospital building was constructed. A large number of beds are reserved for charity cases. In 1931 special clinical and research laboratories were constructed.

The Letterman General Hospital (figure 16) is one of the great Army hospitals in the country. It had its

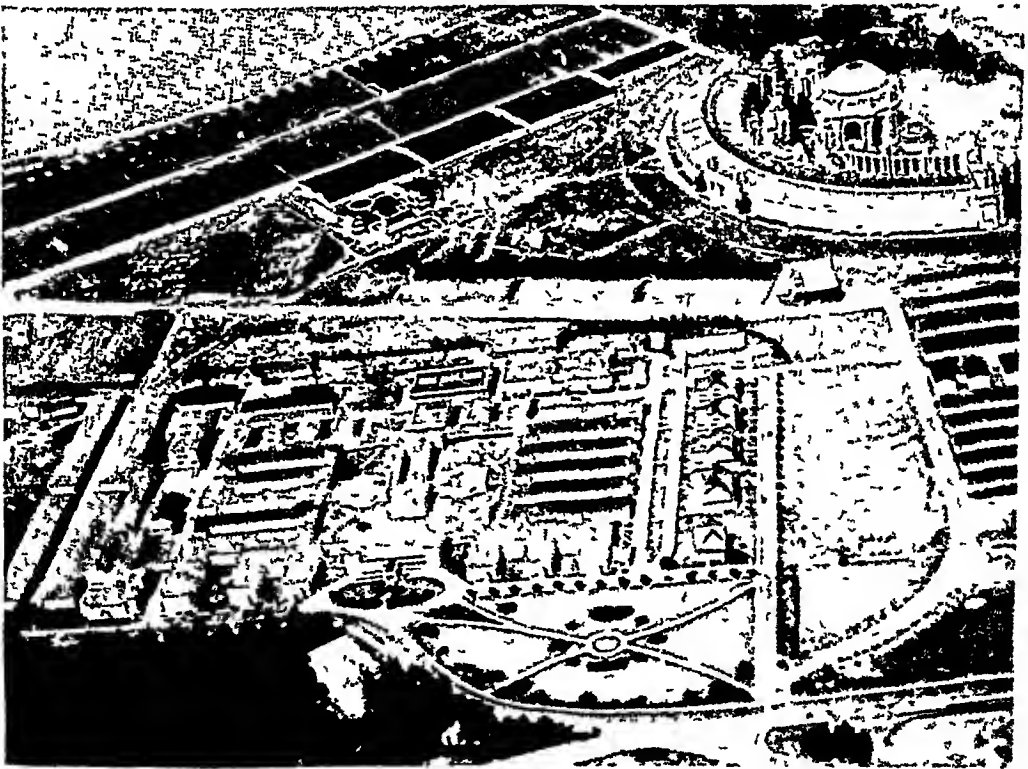


Fig 16 Letterman General Hospital United States- Presidio

origin in 1898 during the war with Spain when the Eighth Army Corps was under mobilization for the First Philippine Expedition. Division field hospitals were found inadequate, and a temporary general field hospital was accommodated in the brick barracks at the Presidio of San Francisco. Later during the same year the War Department established the United States Army General Hospital, although permanent quarters were not begun until 1899. In 1900 a permanent hospital was completed to accommodate 380 patients. In 1911, the War Department designated the new hospital the Letterman General Hospital in honor of the late Major Jonathan Letterman, Surgeon, U.S. Army, who effected the organization of the medical department of the Army of the Potomac during the Civil War. In 1917, the hospital was rapidly ex-

panded by the construction of some 27 temporary buildings to meet the World War conditions. Today it comprises 59 permanent and 26 temporary buildings with a capacity of 965 beds. In addition to serving the military posts of the entire Pacific Coast and of our foreign possessions, accommodations are provided for about 400 beneficiaries of the Veterans' Bureau. The professional service rendered in this hospital has always been of high order.

The St. Francis Hospital (figure 17), organized in 1904, is a general hospital of 325 beds owned and operated by physicians. A number of beds are available for free and part-pay patients.

Mary's Help Hospital (figure 18), conducted by the Sisters of Charity of St. Vincent de Paul, was under construction when the great calamity be-



Fig 17 St Francis Hospital

fell San Francisco in 1906, and the building was entirely destroyed. A new structure was completed in 1912 with 160 beds for all types of patients except those suffering from mental and communicable diseases. A large outpatient department is maintained. The principal aim is to provide efficient and adequate care for the sick poor and for people of moderate means.

The Southern Pacific Hospital was built in 1909 by the Southern Pacific Railroad Company especially to serve the employees of this railway system. The hospital serves as a center for a widespread and coordinated plan to protect the health of its employees and to restore them to usefulness. A large

addition was completed in 1930 which increased the capacity to 500 beds.

The Shriners Hospital for Crippled Children is one of a chain of such hospitals founded and maintained by the Ancient Arabic Order, Nobles of the Mystic Shrine, and located in many cities in America. The San Francisco Shriners Hospital was founded in 1923, with 60 beds, and is devoted to the correction of remedial defects among children under fourteen years of age whose parents or guardians are financially unable to provide the necessary treatment. Children are able to continue their school work while undergoing treatment, through the cooperation of the Board of Education.

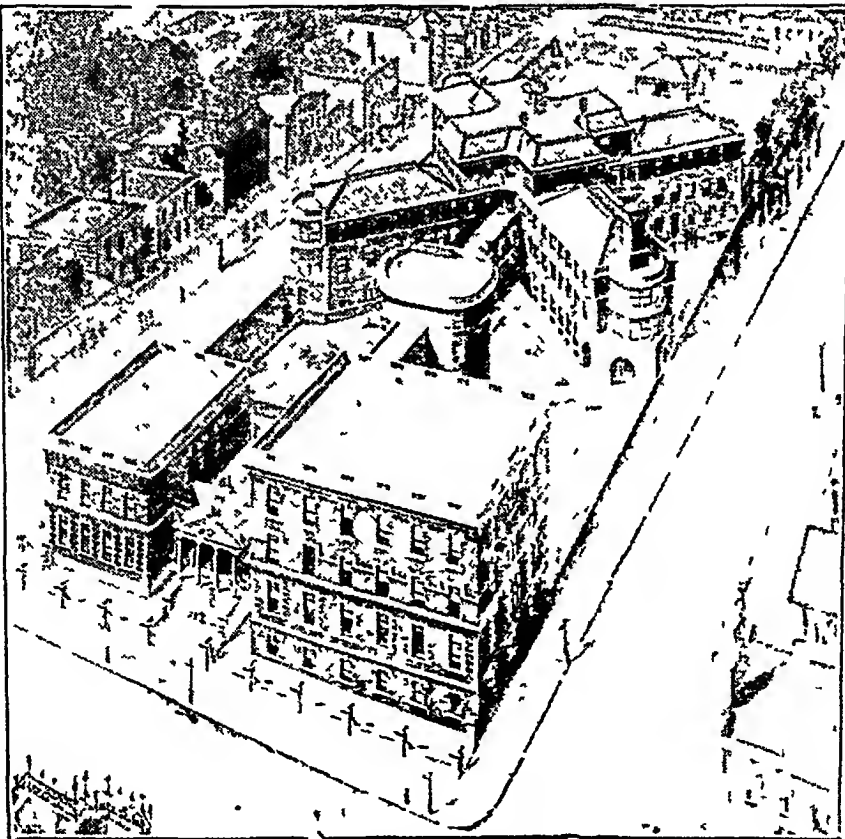


Fig. 18 Mary's Help Hospital

Editorial

MEDICINE TO-DAY AND TO-MORROW

Old General Depression lays his hand heavily on our profession and the average doctor somewhat suddenly awakens to the fact that all is not well and that "something must be done about it"

For some time he has sensed forces at work which, in their operations, were detrimental to him. In a more or less academic way he has read in lay magazines, articles which indicated an unrest on the part of the public, criticisms of the doctor, the hospitals, protests against the cost of medical care. In professional magazines he has read articles by those who are looked upon as leaders of his profession, expressing a concern about the situation, but except where encroachment here and there has hit his income directly, he has gone on his busy way unconcerned, or at least not sufficiently concerned to do more than scold about an irritating situation.

Certainly he has not been truly conscious of the strong social movement which is now in the air. In his address to the College of Surgeons, Dr. Angell speaks of the new philosophy "which conceives the social order as under binding obligation to give its members wholesome conditions of life which conceives human life as indisputably superior to money or physical property in any form." We must listen attentively to his conclusions

that "in the long run, by hook or by crook, society will demand competent medical and nursing service, adequate in amount to meet the needs of everyone. If it cannot secure these as the result of measures voluntarily devised and perfected by the profession and its interested friends, it will look to other agencies, and notably to the Government, to produce the desired results."

The entire world is in a state of flux. In finance, in religion, in constitutional law, as well as in medicine, we seem to be in an irresistible stream, the course of which is uncharted and the end not in sight. It is a period of maladjustment, and a period in which maladjustments long existent are being emphasized. Re-adjustments become a necessity and with these re-adjustments comes the opportunity for the correction of maladjustments, many of them of long standing and of very gradual growth.

It is a time for those who, by reason of official position or by reason of unusual ability, are the leaders of our profession to put their minds together and help us to chart our course. It is not the time for reactionary impulsive action, impractical experiments, or challenging attitudes. We must be on guard against impractical panaceas which come either from within or from without the profession, and hope that no such panaceas will obtain legislative approval.

It is not unlikely that there is to be a distinct change in the character and

type of medical practice in the next generation. A variety of social movements affecting medicine are under way, and their development is not to be stopped. State medicine is edging its way in and is not to be entirely kept out. That concessions must be made, compromises accepted, must be recognized by the rank and file of the profession. It will be the obligation of our leaders to guide, so far as they may, these movements, and to advise us when such concessions are necessary and compromises essential.

The action of the California Medical Society with its proposed public relations office with paid secretary and corps of assistants, and the Michigan plan for a survey of medical activities within the state, indicate that medicine is not unmindful of its obligations.

If state medicine is not to come if institutional practice is not to be more common than it is now, if charitable clinics and governmental medical agencies are not to continue their progressing encroachments, then the rank and file must not be content with this shifting of responsibility to their leaders, but must do their part as individuals. Open warfare against all clinics, good and bad, and social movements of various sorts whose objective is the care of the sick, will not only be futile, but is certain to be detrimental to the entire professional body. Charitable clinics, however much they permit abuses, however much they may impinge on the individual's practice, have a legitimate objective and were started with the best of intentions. Over-enthusiasm sincere enough, and over-ambition on the

part of a paid secretary, are usually responsible for the over-activity and the associated abuses. The individual doctor may do much through personal contact with his acquaintances and patients who are members of lay boards. Properly approached they cannot fail to recognize that the doctor has an interest at least equal to their own in community welfare. It might be well to remind them that these clinics are dependent on the doctor for their very existence, and that the public is today asking the doctor to carry a disproportionate philanthropic load as compared with other individuals in the community.

The obligation rests upon medicine, first, to do its part in making the doctor more competent to fulfill his obligation to his patient and to the community, and second, to direct educational presentations to the public, to the end that the public shall more properly evaluate the doctor's services, and realize the extent of its dependence upon him for good health and happiness. We must have our finger in the pie. Through our representatives we must be in a position to guide where we may this evolutionary process. Society and the profession will equally benefit if this evolution proceeds sanely and along such lines as will permit the medical profession to maintain its ideals and continue to endow mankind with discoveries and with the application of discoveries, such as have, in the past, brought so much of health and happiness into the world. The way must be found for these things to be maintained with the doctor leading a truly independent life assured of sufficient income to make it

possible for him to give the best that medicine has to offer to his patients, and to make life for him reasonably happy and satisfactory. The way will come if the profession will only maintain a unified front. We have ever shown a lack of real cohesiveness. Individualists by training and temperament, we have never been willing to play the game as a group. As this

new social order comes into being, adjustments will be difficult, and some sacrifices will be necessary and imperative. This must be recognized and accepted.

(Contributed editorial by BURTON R. CORBUS, B.S., M.D., F.A.C.P., Chairman of the Executive Committee and of the Council of the Michigan State Medical Society.)

Abstracts

Climate as a Potential Factor in the Etiology of Exophthalmic Goiter and the Other Metabolic Diseases. By C. A. MILLS, M.D. *Endocrinology*, 1932, xvi, 53-63.)

The geographical distribution of exophthalmic goiter, when correlated with possible specific factors, may yield information of value in respect to the etiology of this disease. This is a field of investigation which is far from being exhausted. A simultaneous study of other diseases of endocrine dysfunction and of metabolic exhaustion, such as diabetes and pernicious anemia, should be of value as a control. Using mortality statistics as a basis, and calculating the deaths from each disease as a percentage of the total number of deaths in given areas, distribution maps have been prepared for North America, and likewise climate maps of the continent with special reference to storm areas, storm frequencies, and day-to-day variability of the temperature. From such maps it is observed that the three diseases named are most severe in two areas, one centering around the Great Lakes region, and the other covering the Pacific Northwest from San Francisco northward. The death rates in these regions for these diseases are very much higher than they are in the southern states or in the far north. The highest rates are found in the Great Lakes region where the total death rate from all causes is low and the death rate from the various acute infectious diseases no higher than elsewhere. Climate maps show the Great Lakes area to possess the highest

storm frequency to be seen anywhere in the northern hemisphere, and to have great temperature variability as compared to the South. The Pacific coast, from San Francisco northward, shows a low variability of temperature and few storms, but remains at all times of the year within the limits of the optimum for human activity. It thus appears that the maximum metabolic breakdown occurs in the two areas where climatic stimulation of humanity is the greatest. It would seem that excessive stimulation may be the basic factor which brings a small number of people too near the limits of their metabolic capacity.

The Incidence and Situation of Myocardial Infarction in One Thousand Consecutive Postmortem Examinations. By ARLIE R. BARNES, M.D., and RALPH G. BALL, M.D. (*Am. Jr. Med. Sc.*, 1932, clxxxiii, 215-225.)

Myocardial infarction was recognized grossly in the hearts of 49 subjects in a series of 1000 unselected consecutive postmortem examinations. Only two examples were found in the hearts of 315 patients less than 40 years of age. When this group is excluded, the gross incidence of 4.9 per cent is increased to 6.86 per cent. Forty of the subjects with myocardial infarction were men. One had had a definite history of syphilis, a second, a questionable history of syphilis, and a third had had a positive Wassermann reaction upon the blood and spinal fluid and definite neurological evidence

of syphilis of the central nervous system. Five patients had given histories of angina pectoris, or dyspnea, or both, preceding the signs and symptoms indicative of the first coronary occlusion. In 24 there had been a definite history of coronary occlusion. Of 12 in whose hearts multiple myocardial infarctions were found, 9 had given histories of a second coronary occlusion. As to location, myocardial infarction was observed in the posterior basal portion of the left ventricle in 24 instances and in the apex and anterior portion of the left ventricle in 28 instances. Combining the cases in which actual occlusion of an artery was demonstrated with those in which the artery concerned was identified by dissection although the point of occlusion was not proved, it was found that the anterior descending branch of the left coronary artery was responsible for gross myocardial infarction in 28 instances, the circumflex branch, in 17, and the right coronary artery, in 20. More careful pathologic study of the posterior basal portion of the left ventricle is urged in order that infarctions in that region may not be overlooked. The designation of the left coronary artery as "the artery of coronary occlusion" is no longer justifiable.

A Clinical Study of Etiology of Gastric and Esophageal Carcinoma By LLOYD F CRAVER, M.D. (Am Jr Cancer, 1932, xvi, 68-102)

A group of 36 patients having cancer of the stomach and another group of 18 having cancer of the esophagus provide the clinical material used in this study. In addition to the family history, detailed inquiry was made in regard to 16 points in the previous life of each patient. Ten of these points were concerned with food factors, including the use of alcohol, water, size of meals, rapidity of eating, heat of ingesta, coarseness of foods, amount of seasoning, irregularity of meals, dental disease and presence or absence of teeth. The remaining factors were drug consumption, particularly as concerned cathartics, history of other gastro-intestinal diseases, sinusitis and tonsillitis, and evidence of arteriosclerosis. These factors were as-

signed graded values for each patient, and when the two groups were compared definite discrepancies were found between the factors receiving the higher scores in cases of carcinoma of the stomach and those receiving the higher scores in cases of carcinoma of the esophagus. For cancer of the stomach, the following factors stood in the higher ranks: poor teeth, lack of teeth, other gastro-intestinal diseases, heat of ingested food and drink, irregularity of meals, lack of water, seasoning, drugs (cathartics), rapid eating, tobacco, and alcohol, in the order named. For cancer of the esophagus, the following factors attained the higher scores: tobacco, alcohol, lack of water, poor teeth, lack of teeth, and drugs (cathartics). While the groups concerned are probably too small to permit the drawing of definite conclusions, the method is one which promises data of great value in respect to the etiology of these forms of carcinoma. It is pointed out that it was primarily by this method that the extrinsic factors in the causation of industrial cancers of the skin and bladder were discovered.

Reasons for the Use of Carbon Dioxide with Oxygen in the Treatment of Pneumonia By YANDELL HENDERSON, Ph.D. (New England Jour of Med, 1932, ccvi, 151-155)

The tent method of administering inhalation treatment to pneumonia patients seems to be establishing itself as the best under most circumstances. Intranasal insufflation is generally much less effective in overcoming cyanosis and involves considerable waste of gas. Febrile patients, already experiencing a feeling of suffocation, object to a mask held over the face. Oxygen chambers are expensive and also involve a serious fire hazard. In this article a tent is illustrated which is designed particularly for the administration of a mixture of oxygen and carbon dioxide, now generally termed "carbogen." The use of carbon dioxide and oxygen in combination in the inhalation treatment of pneumonia affords the following advantages:

"(1) Deeper breathing is induced which prevents the development of occlusion and

tends to open parts of the lungs already occluded

(2) Under inhalation of carbon dioxide, morphine or other narcotic drugs may be used more freely to counteract excitement and restlessness. The stimulus to respiration afforded by carbon dioxide tends to counteract the depression of breathing which such drugs otherwise induce.

"(3) Carbon dioxide in solution becomes carbonic acid and tends to exert a bactericidal action upon the pneumococcus and a resolving action upon the pneumonic exudate. These effects are best obtained when inhalation of carbon dioxide is combined with administration of morphine or other narcotic and respiratory depressant drugs. While carbon dioxide tends to lower the pH of the blood and of the pneumonic exudate, it does not decrease the blood alkali or tend to induce an acidosis, but rather the contrary."

Nodular Hyperplasia of Adrenal Medulla in Hypertension. By M. A. GOLDZIEHER, M.D. (Endocrinology, 1932, xvi, 20-28)

The list of cases of pheochromocytoma tumors occurring in patients with hypertension has been increased to include at least 42 examples. In several instances the

diagnosis has been made during life, and surgical removal of the tumor with relief of symptoms has been accomplished. This seems to argue rather strongly for the conception that an excessive amount of chromaffin tissue, such as is represented by these tumors, is capable of producing symptoms of hypertension, to be followed by lesions of the arteries. The evidences that the adrenals may play a part in the pathogenesis of hypertension and arteriosclerosis have been grouped under four heads: increased adrenalin content of the glands, hypertrophy of the musculature of the adrenal veins, morphological changes in the adrenal cortex, and diffuse hyperplasia of the adrenal medulla. In the present paper a nodular hyperplasia of the chromaffin tissue is described. In each of four cases, one or more nodular formations were found in the adrenal medulla, associated with a diffuse hyperplasia. Two of these cases, clinically, gave evidence of high blood pressure. As to the other two, the author believes that sclerosis of the aorta and of peripheral arteries was sufficient evidence that hypertension had existed previously. Further anatomical studies will be needed to determine the extent to which the changes described in this paper are found in association with hypertension.

Reviews

Asthma and Hay Fever in Theory and Practice Part I Hypersensitiveness, Anaphylaxis, Allergy. By ARTHUR F. COCA, M.D., Professor of Immunology, Cornell University Medical College, Clinical Professor in Medicine-elect, New York Post-Graduate Medical School. Editor of The Journal of Immunology. *Part II Asthma.* By MATTHEW WALZER, M.D., Instructor in Applied Immunology, Cornell University Medical College, Deputy Attending Physician, Clinic of Applied Immunology, New York Hospital, Chief of Allergy Clinic, Jewish Hospital of Brooklyn. *Part III Hay Fever.* By AUGUST A. THOMMEN, M.D., Lecturer in Medicine, University and Bellevue Hos-

pital Medical College, Director of the Allergy Clinic, Medical College Dispensary, New York University. xxiv + 851 pages, 95 figures, numerous tables and charts. Charles C. Thomas, Springfield, Illinois, 1931. Price, \$8.50.

The writer reviews this book with enthusiasm. It gives a very thorough, studious and scholarly review of the entire field which its title and sub-titles indicate. So complete and comprehensive is it, that a review dealing with single phases of the subject seems inappropriate. Whether etiology, pathology, diagnosis and testing, microbiology or treatment, happens to be the reader's quest, he will find here a critical monographic presentation of the de-

sired subject matter. Certain minor points will be questioned by other workers in this field. In fact, the three authors acknowledge the inevitable lack of complete accord which exists among themselves. This is in itself a pledge of honest, scientific workmanship. The use of a compact type face, with much quoted matter in a smaller type than the body of the text, has made it possible to put an unusual amount of information between one pair of book covers. Extensive bibliographic lists are provided, with 400 titles under Part I, 1077 under Part II, and 628 for Part III. The index is conveniently divided into two parts, one is a general index and the other a special list of atropens and excitants. This book should be in the intimate library of everyone working in the field of allergic disease. Its value will be appreciated by the clinician as well as by the investigator in the laboratory.

Heart Disease. By PAUL DUDLEY WHITE, M.D., F.A.C.P., xvii + 931 pages, 119 illustrations, 9 tables. The Macmillan Co., New York City, 1931. Price, \$12.00.

This volume, one of the Macmillan Medical Monographs, is an exhaustive, logical and competent treatment of the subject, and might well have been entitled "Cardiovascular Disease" since the author, realizing the inseparability of diseases of the heart proper from those of the blood vessels, has wisely treated of both, although the emphasis is placed upon affections of the heart itself. Divided into four major parts, the content of the book is available for either reference or textual use. The material is carefully outlined and lucidly presented so that a minimum of time is required to find the discussion of any given topic. The first major division comprises a manual for the conduct of the clinical investigation, including suggestions for record forms, methods of history taking and general procedures of bedside and laboratory examination with special reference to the various maneuvers useful in cardiological study. Separate chapters are devoted to cardiovascular roentgenology and electrocardiography. Numerous illustrations of excellent quality add to the clarity of the text. Part II is a systematic treat-

ment of the etiological factors of heart disease. Here, necessarily, the arrangement and attack are somewhat arbitrary, but the reader will readily find that his fields of special interest receive just consideration although it may be that the scheme of classification is unlike that to which he has been accustomed.

Morphological abnormalities of the heart are considered in Part III. This is the least satisfactory section of the book. In a text of this size, one might expect this phase of the subject to be treated in a much more comprehensive manner. This lack is especially evident in the discussion of the pathology of cardiac syphilis. The author has evidently labored under a sense of restraint lest the section on morphological pathology become unduly large. Fuller descriptive treatment and the addition of more illustrations in this part would have been of advantage to many readers. Part IV is devoted to the consideration of disorders of the heart which are primarily functional and which are not necessarily conditioned upon demonstrable structural abnormality. Inevitably, Parts III and IV overlap somewhat but the division of material in this manner enhances the orderliness of the presentation and also facilitates the use of the book for reference purposes. The prognosis and treatment of the various disorders are to be found under the specific topics and no especial section is devoted to therapy. This procedure tends to avoid repetition and is conducive to compactness of arrangement. An extensive bibliography, requiring nearly 200 pages, is appended, and to those engaged in cardiological work, this portion alone is worth the cost of the volume. The space occupied by this section might have been much reduced by using a smaller type face, without impairing its value. The reviewer would have gladly accepted this space economy in the interest of a fuller treatment in Part III. The Index is unusually well planned and has proven adequate when put to repeated tests.

Simplified Diabetic Management. By JOSEPH T. BEARDWOOD, JR., A.B., M.D., F.A.C.P., Chief of Diabetic Clinic and Associate Visiting Physician, Presbyterian Hospital.

in Philadelphia; Physician in Chief to the Department of Metabolic Diseases, Abington Memorial Hospital, Associate in Cardiology, Graduate School of Medicine, University of Pennsylvania, and HERBERT T KELLY, M D, A A C P., Associate in Diabetic Clinic, Presbyterian Hospital in Philadelphia, Associate in Cardiology, Graduate School of Medicine, University of Pennsylvania, and in The Philadelphia General Hospital, Diets prepared with the collaboration of Elsie M Watt, A B, formerly Dietician, Diabetic Clinic, Presbyterian Hospital in Philadelphia 191 pages, illustrations, folding chart J P Lippincott Company, Philadelphia Price, \$1 50

This book is arranged in three chapters and is primarily for the patient In the first there is a simple statement of the nature of diabetes, of the dietetics of this disease and of the unit method of planning the menu of the diabetic Here also is found information in regard to insulin and its use The second chapter is written with the needs and interests of the more intelligent "well-trained" diabetic in mind, while in the third are grouped the various tables of food values, recipes and suggested menus For the more intelligent patient this book will be of interest and values Others are apt to be discouraged by the apparent complexity of the "Diet Prescription Chart" and its application A few minutes study will show that this complexity is more apparent than real

The Modern Therapeutics of Internal Diseases An introduction to Medical Practice By A P CAMADIAS, O B E, M D (Durh and Paris), M R C P (London), formerly Chief of the Therapeutic Clinic of the Faculty of Medicine of the University of Paris, formerly Senior Physician and Lecturer for Internal Diseases, Evangelismos Hospital, Athens x1 + 147

pages William Wood and Company, New York, 1931 Price, \$3 75 net

The presentation of a philosophy of therapeutics is the aim of this book, thus the purchaser who expects specific advice for the therapy of disease may feel that he has been deceived by the title The thesis that there are no diseases, but only diseased individuals, is stressed throughout Certainly, there is nothing new in this conception but there is much to be gained by keeping it in mind The style is heavy, somewhat involved, and reminiscent of a preceding century In the few instances in which the author leaves the realm of the abstract some rather unusual pronouncements appear On page 118, it is stated that glandular organo-therapeutical preparations are of the greatest importance in the treatment of *tetanus* Doubtless *tetany* was intended Colloidal gold is said to provoke principally the production of antityphoid antibodies Aside from its emphasis upon the individual as a whole and the importance of constitution, this book has but little to recommend it to the American physician

Die Verkalkung der Gewebe By Dr GEORGE MEYER ZU HORSTE 74 pages, 10 illustrations S Karger, Karlstrasse 59, Berlin, 1932 Price, 7 M

This monograph is based upon an experimental investigation of the factors influencing the deposition of lime salts in tissue Rachitic epiphyseal sections from young rats which had been on McCollum diet No 3143 were immersed in Shipley's solution, with such chemical-physical alterations in the solution as were under investigation The deposition of lime salts in the test object and the changes in the medium were studied quantitatively by appropriate methods This work will be of considerable importance to those engaged in research in the fields of physiological and pathological calcification

College News Notes

AN URGENT RESPONSIBILITY OF FELLOWS AND MASTERS

Candidates for membership, either Associateship or Fellowship, in the American College of Physicians, must be proposed, seconded and endorsed by Fellows or Masters of the College in a manner prescribed by the By-Laws. When such proposals are filed in the office of the Executive Secretary, a card of notification of said proposal is sent to every Fellow and Master residing in the district from which the candidate comes. This notification card requests each Fellow or Master to file immediately in the office of the Executive Secretary information for or against the election of said candidate. Communications are treated as strictly confidential, being referred no further than to the Committee on Credentials.

These announcement and inquiry cards are of great assistance to the Committee on Credentials when reviewing the candidates for election. In most localities, Fellows and Masters carefully fulfill their responsibility by furnishing information about each candidate but many times these cards are not promptly returned, or not returned at all. Some apparently have assumed that if they do not know the candidate, or if they do not favor his election, they should not return the card at all. The Committee intends that all cards be returned whether the candidate is known or not. It is at least of assistance to ascertain how widely the candidate is known among the Fellows and Masters of the College in his district or state.

The Committee on Credentials expends much time and honest effort in determining the qualifications of candidates for election. Members will assist tremendously by promptly returning all inquiry cards after noting thereon their unbiased opinion of the candidate's qualifications for election.

NOMINATIONS FOR ELECTIVE OFFICERS

1932-1933

The Nominating Committee herewith transmits the following nominations for elective officers of the American College of Physicians for the year 1932-1933

President-Elect—George Morris Piersol, Philadelphia, Pa

1st Vice President—Maurice C Pincoffs, Baltimore, Md

2nd Vice President—Charles G Jennings, Detroit, Mich

3rd Vice President—Noble Wiley Jones, Portland Ore

Respectfully submitted

Alfred Stengel, Chairman

February 19 1932

ABSTRACT OF MINUTES MEETING OF THE BOARD OF REGENTS

Chicago, Ill,

December 20, 1931

The Board of Regents of the American College of Physicians was called to order in Room 325, Drake Hotel, Chicago, Illinois, at 9 50 A M by the President, Dr S Marx White, Minneapolis, Minnesota

The following were present Drs S Marx White, Francis M Pottenger, Charles G Jennings, Clement R Jones, George Morris Piersol, David P Barr, James B Herrick, Maurice C Pincoffs, Walter L Bierring, George E Brown, John H Musser, O H Perry Pepper, James H Means, James Alex Miller, Sydney R Miller, W Blair Stewart, Carl V Weller (Editor of the Annals of Internal Medicine), and Mr E R Loveland, Executive Secretary

Extracted minutes of the previous meeting were read by the Executive Secretary and approved

The Executive Secretary reported the receipt of communications from Drs J A Lichty, A R Elliott, N W Jones, J R Arneill, J C Meakins and James S McLester expressing regret at inability to be in attendance at the meeting

The following deaths since the last Regents' meeting were reported by the Executive Secretary

Fellows

Leonard Napoleon Boston	Philadelphia, Pa	July 4, 1931
Lawrence Evans Chapman	Galveston, Texas	October 21, 1931
Edward Tyler Edgerly	Ottumwa, Iowa	November 13, 1931
Thompson Frazer	Newark, N J	October 9, 1931
Harry M Hall	Wheeling, W Va	June 5, 1931
Horace Howard Jenks	Philadelphia, Pa	July 6, 1931
Bradford Churchill Loveland	Syracuse, N Y	June 25, 1931
John F W Meagher	Brooklyn, N Y	August 25, 1931
Leonard Milton Murray	Toronto, Ont	August 8, 1931
James Percy Schureman	New Brunswick, N J	May 6, 1931
Arthur Clifford Selmon	Battle Creek, Mich	May 16, 1931
William Stephens Shields	Denver, Colo	August 6, 1931
Elmore Callaway Thrash	Atlanta, Ga	June 22, 1931
Henry Lyle Winter	Newburgh, N Y	July 29, 1931

Associates

Robert Gibbs Douglas	Shreveport, La	July 23, 1931
Theodore Leacraft Hein	New York, N Y	September 25, 1931
William A Monroe	Sanford, N C	1927
Edward Peter Schatzman	Pittsburgh, Pa	July 27, 1931
Joseph Witham Young	Toledo, Ohio	July 14, 1931

The following resignations were accepted

Dr Frank M Conlin (Fellow), Omaha, Nebr

Dr Henry D Jump (Associate), Philadelphia, Pa

Dr William R Perkins (Associate), Washington, D C

Dr James Steele, Brooklyn, N Y, was reinstated as a Fellow of the College

The Executive Secretary presented an advertisement which has appeared in several Cleveland and Pittsburgh newspapers, as well as others, by the G R Pilgren Company, referring to "Professor Ernest S Bishop, M D, Fellow of the American College of Physicians" It was pointed out that Dr Bishop had been a Fellow of the College, but that he has been dead for several years The Pilgren Company is now operated by Dr Bishop's widow, Helen E Bishop Mrs Bishop had been requested to discontinue reference to Dr Bishop as a Fellow of the American College of Physicians, especially in the present tense, but she had indicated no willingness to discontinue reference to the American College of Physicians, but expressed a willingness to change the tense to past tense

Upon motion by Dr James Alex Miller, seconded by Dr Means, and unanimously adopted, it was

RESOLVED, to have the Executive Secretary consult C Berkeley Taylor, Esq, of Philadelphia, concerning an opinion as to what action may be taken by the College to restrain the Pilgren Company from using the name of the American College of Physicians in its advertisements, and authorizing the Executive Secretary to pay whatever legal fee is necessary

President White reported the receipt of the report on Pediatric Education by the Committee on Medical Care for Children, White House Conference on Child Health and Protection, and briefed the recommendations contained on Pages 93 and 94 of that report

Upon motion by Dr Pineoffs, seconded by Dr C R Jones, and unanimously carried, it was

RESOLVED, that the report on Pediatric Education by the Follow-Up Committee on Section I, White House Conference on Child Health and Protection, be referred to the Committee on Public Relations with power to act, with the suggestion that the Committee may use the editorial page of the Annals of Internal Medicine as a means of expressing the sentiment of the College

Dr Piersol, Chairman of the Committee on Credentials, reported at length on the matter of the admission of candidates from the Medical Corps of the U S Army, U S Navy, and U S Public Health Service In an effort to revise the procedure to the satisfaction of the Surgeons General and of the College, President White had arranged a conference between Surgeon General Patterson of the Army and the Committee Surgeon General Patterson being unable to personally attend, appointed as his substitute, Colonel Hutton, Chief Surgeon of the Sixth Corps Area A meeting with Colonel Hutton, at which Dr Piersol, Dr S R Miller and President White were present, was held at the Drake Hotel, Chicago, on December 19 The recommendations of the Committee, to which Colonel Hutton agreed, are embodied in the following resolution, which was unanimously adopted

RESOLVED, that in the future in dealing with Officers of the Army, Navy and Public Health Service, recommendations of the Surgeon General of each respective service be accepted as sufficient qualification for candidacy of such Officers

Dr Piersol, as Chairman of the Committee on Credentials for Fellowship, presented the following list of candidates whose credentials the Committee had found adequate and whom they recommended to Fellowship On resolution regularly made seconded and unanimously carried, the following candidates were elected to Fellowship

ELECTED TO FELLOWSHIP

December 20, 1931

ALABAMA

Selma

James Fairly Alison

*1 John A Lanford

*2 Charles J Bloom

*3 Fred Wilkerson

CALIFORNIA

Los Angeles

Leland Stanford Chapman

1 Samuel M Alter

2 Ernest C Fishbaugh

3 Egerton Crispin

Robert William Langley

1 A J Scott, Jr

2 Henry Snure

3 Egerton Crispin

Burrell Otto Raulston

1 F M Pottenger

2 George G Hunter

3 Egerton Crispin

Bertnard Smith

1 F M Pottenger

2 George G Hunter

3 Egerton Crispin

Howard Frank West

1 F M Pottenger

2 George G Hunter

3 Egerton Crispin

Oakland

Albert Holmes Rowe

1 Ernest H Falconer

2 W W Boardman

3 H Lisser

Piedmont

Stewart Vernon Irwin

1 Ernest H Falconer

2 Arthur M Smith

3 H Lisser

San Francisco

Fred Firestone

1 Wm. C Voorsanger

2 Arthur L Bloomfield

3 H Lisser

Jacob Casson Geiger

1 Ernest H Falconer

2 W W Boardman

3 H Lisser

Samuel Hayman Hurwitz

1 W W Boardman

2 Ernest H Falconer

3 H Lisser

Fred Herman Kruse

1, Ernest H Falconer

2 Wm J Kerr

3 H Lisser

Henry George Mehrtens

1 W W Boardman

2 Ernest H Falconer

3 H Lisser

Harry Clare Shepardson

1 Ernest H Falconer

2 R J Reitzel

3 H Lisser

Sidney Jerome Shipman

1 Ernest H Falconer

2 Philip H Pierson

3 H Lisser

San Jose

George Alexander Gray

1 Frank R Bealer

2 Wm H Strietmann

3 H Lisser

COLORADO

Colorado Springs

Alan Callender Sutton

1 Allen K Krause

2 W Paul Holbrook

3 W Warner Watkins

Cragmor

Alexius Mador Forster

1 T R Love

2 J H Brown

3 J N Hall

CONNECTICUT

Meriden

Ralph de Ballard Clarke

1 Thomas P Murdock

2 Cole B Gibson

3 Henry F Stoll

New Haven

Louis Herman Nahum

1 George Blumer

2 Francis G Blake

3 Henry F Stoll

*1 Proposer, 2 Second, 3 Endorser

DISTRICT OF COLUMBIA

Washington

Irving William Jacobs

1 L L Pratt

2 C S Butler

3 C E Riggs

Earl Baldwin McKinley

1 Bailey K Ashford

2 P Gutierrez Igaravidez

3 M Roses Artau

Robert Urie Patterson

1 Wm Gerry Morgan

2 Percy M Ashburn

3 C E Riggs

FLORIDA

St Petersburg

Roscoe Hosmer Knowlton

1 W C Blake

2 L Limbaugh

3 T Z Cason

ILLINOIS

Chicago

Allan Joseph Hruby

1 Frank Smithies

2 Frederick Tice

3 James G Carr

William Henry Walsh

1 Joseph A Capps

2 Benjamin Goldberg

3 James G Carr

Elgin

Jay MacDonald Milligan

1 S L Gabby

2 James G Carr

3 James B Herrick

INDIANA

Evansville

Shelby William Wishart

1 Frank N Wilson

2 George R Herrmann

3 Roscoe H Beeson

IOWA

Dubuque

Frank Patrick McNamara

1 Daniel J Glomset

2 L R Woodward

3 Walter L Bierring

Iowa City

Herbert William Rathe

1 John H Peck

2 Fred M Smith

3 Walter L Bierring

Frank James Rohner

1 Fred M Smith

2 John H Peck

3 Walter L Bierring

KENTUCKY

Lexington

Edward James Murray

1 John W Scott

2 John Harvey

3 Ernest B Bradley

LOUISIANA

Baton Rouge

Cecil Oliver Lorio

1 Lester J Williams

2 Charles J Bloom

3 John H Musser

New Orleans

John W Williams

1 Charles W Duval

2 John A Lanford

3 John H Musser

MASSACHUSETTS

Brockton

Harrison Ayer Chase

1 Elliott P Joslin

2 Joseph H Pratt

3 Roger I Lee

MICHIGAN

Ann Arbor

Margaret Bell

1 Cyrus C Sturgis

2 Frank N Wilson

3 James D Bruce

William Morgan Brace

1 Cyrus C Sturgis

2 Carl V Weller

3 James D Bruce

Grand Rapids

Faith Frances Hardy

1 Wm R Vis

2 Thomas D Gordon

3 James D Bruce

Grosse Pointe

Silas Willard Wallace

1 Frank J Sladen

2 Alpheus F Jennings

3 James D Bruce

Houghton

Robert Bruce Harkness

1 Salvatore Lojaco

2 F Herbert Bartlett

3 James D Bruce

MINNESOTA

Minneapolis

- Wilhelm S Anderson
 1 Arthur A Wohlrabe
 2 J Arthur Myers
 3 Edward L Tuohy

MISSISSIPPI

Gulfport

- William Albert Dearman
 1 Seale Harris
 2 Felix J Underwood
 3 G W F Rembert

University

- Peter Whitman Rowland
 1 Felix J Underwood
 2 N C Womack
 3 G W F Rembert

MISSOURI

Independence

- George Thomas Twyman
 1 D D Stofer
 2 W W Duke
 3 A C Griffith

St Louis

- Ralph Aloysius Kinsella
 1 A P Munsch
 2 C U Neilson
 3 A C Griffith

Springfield

- George Bruce Lemmon
 1 E S Smith
 2 J Curtis Lyter
 3 A C Griffith

NEBRASKA

Omaha

- Maurice Cronin Howard
 1 Floyd Clarke
 2 John R Kleyla
 3 A Sachs

NEW JERSEY

Asbury Park

- James Franklin Ackerman
 1 William G Herrman
 2 Clarence M Trippe
 3 W Blair Stewart

Freehold

- John Conover Clayton
 1 Clarence M Trippe
 2 James J McGure
 3 W Blair Stewart

Grenloch

- Martin H Collier
 1 Marcus W Newcomb
 2 B S Pollak
 3 W Blair Stewart

NEW YORK

Brooklyn

Franklyn Chapman Hill

- 1 W W Behlow
 2 K C Melhorn
 3 C E Riggs

Harry Robert Litchfield

- 1 Eugene S Dalton
 2 M J Dattelbaum
 3 Luther F Warren

George Henry Roberts

- 1 A F R Andresen
 2 Tasker Howard
 3 Luther F Warren

Irving Jesse Sands

- 1 Simon R Blatteis
 2 Irving Gray
 3 Luther F Warren

Hempstead

Roy Durell Grimmer

- 1 T C Chalmers
 2 Cornelius A O'Leary
 3 Luther F Warren

Loomis

George Foster Herben

- 1 Edward S McSweeney
 2 Lewis A Conner
 3 James Alex Miller

New York

Peter Irving

- 1 Charles A McKendree
 2 Harlow Brooks
 3 James Alex Miller

Emile Gordon Stoloff

- 1 M Murray Peshkin
 2 Albert S Hyman
 3 Luther F Warren

Grant Thorburn

- 1 W P Anderton
 2 Henry T Chickering
 3 James Alex Miller

Smithtown Branch

Guy Hanford Turrell

- 1 Cornelius A O'Leary
 2 Edwm P Kolb
 3 Luther F Warren

Syracuse

William Walter Street

- 1 Edward C Reifensiem
- 2 W J McNerney
- 3 Allen A Jones

NORTH CAROLINA

Charlotte

Douglas Heath Nisbet

- 1 J P Munroe
- 2 A A Barron
- 3 C H Cocke

Edward Jones Wannamaker, Jr

- 1 W O Nisbet
- 2 J P Munroe
- 3 C H Cocke

Durham

William Raney Stanford

- 1 David Riesman
- 2 Thomas Fitz-Hugh, Jr
- 3 C H Cocke

High Point

Frederick Raymond Taylor

- 1 P W Flagge
- 2 Wm deB MacNider
- 3 C H Cocke

Statesville

Corte Long Sherrill

- 1 J P Munroe
- 2 W O Nisbet
- 3 C H Cocke

Winston-Salem

Thomas Craig Redfern

- 1 John K Pepper
- 2 L B McBrayer
- 3 C H Cocke

William DeKalb White

- 1 S D Craig
- 2 L B McBrayer
- 3 C H Cocke

OHIO

Lima

Frederic George Maurer

- 1 C W Waggoner
- 2 John T Murphy
- 3 A B Brower

PENNSYLVANIA

Cresson

Thomas H A Stites

- 1 A S Kedi
- 2 C M Griffith
- 3 E Bosworth McCready

Philadelphia

Joseph Bank

- 1 H L Bockus
- 2 Russell S Boles
- 3 George Morris Piersol

Charles John Haines

- 1 Orlando Petty
- 2 H L Bockus
- 3 George Morris Piersol

Simon Stein Leopold

- 1 Charles W Burr
- 2 Alfred Stengel
- 3 O H Perry Pepper

Abraham Maurice Ornstein

- 1 David Riesman
- 2 Truman G Schnabel
- 3 E J G Beardsley

Pittsburgh

Thomas Edward McMurray

- 1 E M Frost
- 2 S George
- 3 E Bosworth McCready

RHODE ISLAND

Providence

Charles Francis Gormly

- 1 Alex M Burgess
- 2 Wm P Buffum
- 3 Frederic J Farnell

William Sylvester Streker

- 1 William P Buffum
- 2 Alex M Burgess
- 3 Frederic J Farnell

Guy William Wells

- 1 Alex M Burgess
- 2 Wm P Buffum
- 3 Frederic J Farnell

SOUTH CAROLINA

Greenville

Hugh Percival Smuth

- 1 J H Cannon
- 2 Kenneth M Lynch
- 3 Robert Wilson

TENNESSEE

Memphis

John Philips Henry

- 1 William C Chance
- 2 Otis S Warr
- 3 I O Manner

TEXAS

Amarillo

George McClave Cultra

1 John G Young

2 T C Turrell

3 Charles T Stone

San Antonio

John Alexander McIntosh

1. E V. DePew

2 C D Steinwinder

3 Charles T Stone

UTAH

Salt Lake City

Louis Emdred Viko

1 Wm L Rich

2 M M Critchlow

3 G Gill Richards

VIRGINIA

Richmond

Pauline Williams

1 William B Porter

2 Beverley R Tucker

3 J Morrison Hutcheson

WEST VIRGINIA

Huntington

William B Hunter

1. Walter E. Vest

2 C A Ray

3 John N Simpson

WISCONSIN

Milwaukee

Elston Lewis Belknap

1 Arthur J Patek

2 C H. Stoddard

3 Rock Sleyster

John Edwin Habbe

1 T L Squier

2 John Huston

3 Rock Sleyster

MEXICO

Mexico City

William D Nimeh

1 Howard R Hartman

2 H L Bockus

President White reported that the Committee on Annals of Internal Medicine, including Drs Piersol, Barr and himself, had followed the directions of the Board of Regents in carrying on the Annals, and that Dr Weller had continued to act as Editor in a very satisfactory manner. There was some detailed report on President's White's part concerning the progress of the journal and the work of the Committee. He recommended that the present Committee and the present arrangement be authorized to continue at least until the completion of Volume V. The following resolution was regularly adopted.

RESOLVED, that the present Committee on Annals of Internal Medicine shall continue the present arrangement until the completion of Volume V of the Annals of Internal Medicine.

Upon invitation by President White, Dr Carl V Weller, Editor of the Annals of Internal Medicine, was present and made a report upon his work. He stated that because of his close connections previously with Dr Warthin and the editorial office of the Annals, it had been possible for him to take up the editorial work at the various stages of the successive issues without any break.

Dr Weller referred to minor changes in the Annals which had been made, including a uniform paper stock and a reduction in the cost of reprints. A change in paper stock had resulted in a saving of approximately fifty dollars per issue of the journal. He referred also to the adoption of a definite bibliographic style, uniform throughout the journal. He presented a copy of the style sheet for the examination of the Regents. His reasons for adopting this particular style included appearance in type, dignity, and its being in keeping with the style of some of the higher grade European journals. Furthermore, he stated that the adopted style for the Annals has a certain individuality, distinctiveness and personality.

Dr Weller also stated that he had changed the format. The reviews now follow immediately after the abstracts, without any wastage of space. The same is being done in

connection with obituaries in the College News Notes. The printing of the Annals is paid for by the page, and the fewer blank half or quarter pages there are, the greater advantage to the College.

Dr. Weller then reported upon the receipt of papers for publication. He recalled the struggle in the earlier years to secure material enough for even small issues. The situation has utterly changed. On June 1, 1931, there were thirty-five papers on hand. Since then, Dr. Weller had received eighty-two additional scientific papers, making a total of one hundred and seventeen, not including those submitted from the Baltimore Clinical Session. Of the one hundred and seventeen papers, he had returned twenty-three. The increasing number of papers submitted had made it possible to be more and more critical about those accepted. He pointed out that regardless of how tactful an editor tries to be, there will be occasions when the rejection of a paper will aggrieve the author. He had tried to mitigate this in every possible way, particularly by giving constructive criticism. In some instances, authors had rewritten papers according to the suggestions made, and the revised papers had been acceptable for publication. From the above period, he stated he had now ninety-four papers accepted for publication. He stated he had assigned from fifty to sixty per cent of the space in the Annals to papers originating from the General Sessions of the previous Clinical Session. Certain precedence, he stated, should be given to those from the Clinical Session but a part of each journal should be used for papers received from other sources.

Dr. Weller had fifty-three acceptable manuscripts in addition to those received from the Baltimore Clinical Session, and pointed out that this quantity alone would be sufficient to run the journal for five or six months. He expressed the opinion that it is unfortunate that men should have to wait that long a time for publication of their papers. The only remedy would be to reject a larger proportion at the source. Nevertheless, the Archives of Internal Medicine, the journal most nearly comparable to ours, has been publishing articles ten or twelve months after submission.

The cost of the Annals is in proportion to the size of the journal. At the present time an issue of thirty-two hundred per month was being printed. Roughly, an issue of this size costs, per page, ten dollars. Added to this is the additional cost of producing cuts, the cost of distribution, etc. He stated that he has been making a study of reducing cuts to a minimum number, and also reducing the area or size of cuts wherever there would be no great disadvantage. Dr. Weller stated that the cost of printing had been increased \$1,659.85 for the seven months of the previous year. However, there had been one hundred and forty-eight more pages, an increase of about one-sixth in the content.

In his closing comments, Dr. Weller said "with the obvious continuous growth in prestige, power and membership on the part of the College, I do not see why the Annals should not be made the best journal on Internal Medicine in this country, if not in the world."

President White, acting as Chairman of the Committee on the Annals, stated that the Committee had felt that its function is primarily that of the selection of the Editor, and that the Committee has had no active function in relation to editorial management. The selection of the Editor and the continuance of the policies of the Annals had been the Committee's most important function. However, the Committee would want to aid the Editor in any manner he desires. President White took the opportunity to thank Dr. Weller for his extremely efficient management of the Annals, and stated that throughout the membership, it has been commented among those who have been watching the Annals that the journal has gone on without any disruption, and the journal has been growing, improving in appearance, extending its influence and taking a more decided place in medical literature in this country.

The Executive Secretary distributed mimeographed copies of the Cost Analysis of the Annals of Internal Medicine, and discussed the report in detail. The official report will be

included with the annual report submitted at the San Francisco Clinical Session, and therefore, is not reproduced here

The Executive Secretary reported that two issues of the Annals of Internal Medicine are exhausted—November, 1928, and February, 1931. The November, 1928, issue had been exhausted, due to unusually heavy demands for that issue, but the February, 1931, issue had been exhausted through some unexplained shortage in the printing office. Mr. Wiltse, Manager of the Ann Arbor Press, although he had but recently assumed such office, reported a willingness to reprint the February, 1931, number, if necessary, without cost to the College.

On motion by Dr. Brown, seconded by Dr. C. R. Jones, and unanimously carried, it was **RESOLVED**, that the Executive Secretary be instructed to advertise for fifty copies of the February, 1931, issue of the Annals, in an effort to replenish the stock, and that the cost of such advertising should be allocated to the Ann Arbor Press.

The allocation of cost to the Ann Arbor Press was included in the resolution only after it had been pointed out that it would be much less expensive to the Ann Arbor Press for us to secure these additional copies through advertising than by asking them to reprint the issue.

There was a complete discussion of the possibility of the College publishing the Clinics delivered at its Clinical Sessions. Dr. O. H. Perry Pepper and the Executive Secretary had assembled a quantity of facts concerning the possible publication of such Clinics by some of the leading medical publishers. Most of them expressed little or no interest in the project unless the College would subsidize the publication of such Clinics to such a degree as to guarantee a minimum distribution, possibly of two thousand to twenty-five hundred copies.

Upon motion by Dr. Musser, seconded by Dr. S. R. Miller, and unanimously carried, it was

RESOLVED, that the publication of Clinics by the College be deferred for at least another year.

Dr. C. R. Jones, as Chairman, presented the report of the Finance Committee. He presented a plan limiting the traveling expenses to and from meetings by Officers and members of the Board of Regents, which is embodied in the following resolution which was adopted following a motion by Dr. Piersol, seconded by Dr. Stewart.

RESOLVED, that the traveling expenses of Officers and members of the Board of Regents shall not exceed Five Dollars a day in excess of railroad fare and lower berth when traveling, and shall not exceed Ten Dollars a day during the stay at the place of meeting, this resolution to become effective as of December 19, 1931.

Dr. Jones then suggested the desirability of authority from the Board of Regents for him and the Secretary-General to complete an agreement with the Commonwealth Trust Company, of Pittsburgh, to act as custodian of the securities owned by the College, such agreement to be like that which was authorized at the previous meeting with the Bank of Pittsburgh.

Upon motion by Dr. James Alex. Miller, seconded by Dr. Pepper, and unanimously carried, it was

RESOLVED, that the Secretary-General and Treasurer be authorized to complete a trust agreement with the Commonwealth Trust Company to act as custodian of the securities belonging to the College, collect the coupons, etc., in a similar manner to the previous contract with the Bank of Pittsburgh.

AMERICAN COLLEGE OF PHYSICIANS, INC
Balance Sheet, December 31, 1931

ASSETS

Cash			
In Bank and on Hand	\$14,594 77		
In Banks in Hands of Receivers			
The Highland National Bank, Pittsburgh	\$11,627 20		
The Bank of Pittsburgh, Pittsburgh	9,746 45		
Exchange National Bank, Pittsburgh	5,830 68	27,204 33	\$41,799 10
Investments (See Schedule No I)			61,496 73
Accrued Interest on Investments			905 63
Inventory of Keys, Pledges, Frames, etc			500 92
Deferred Expenses for the Sixteenth Annual Clinical Session (Paid in Advance of 1932)			3,275 10
Furniture and Equipment	3,616 92		
Less, Allowances for Depreciation	1,225 77	2,391 15	\$110,368 63

LIABILITIES

Accounts Payable	125 00		
Deferred Income			
Advance Collections for Exhibits, Sixteenth Annual Clinical Session	359 13		
Advance Subscriptions for Volume VI, Annals of Internal Medicine	317 79		801 92
Excess of Assets over Liabilities			\$109,566 71

FUNDS

Endowment Fund (See Schedule No II)	\$52,400 00		
General Fund (See Schedule No III)	57,166 71		109,566 71

SCHEDULE No I
INVESTMENTS
December 31, 1931

Par Value	Bonds	Cost
\$ 3,000	Borough of Steelton, Pa, 4½s, 1933	\$ 3,071.25
4,000	Canadian National Railway, 4½s, 1956	3,930 00
5,000	Canadian National Railway, 5s, 1969	4,987 50
2,000	Canadian National Railway, 5s, 1969	2,055 00
2,000	Canadian National SS Co, 5s, 1955	2,040 00
2,000	City of Covington, 4¾s, 1946	2,134 01
2,000	City of Detroit, 4¾s, 1944	2,010 40
2,000	City of Detroit, 4¾s, 1949	2,025.26
2,000	City of Houston, 4¾s, 1942	2,077 50
2,000	City of Los Angeles, 5s, 1943	2,158.24
1,000	City of Montreal, 5s, 1956	1,071 30
2,000	City of Newark, 4½s, 1944	2,075 00
10,000	City of Philadelphia, 4½s, 1979	10,225 00
2,000	City and County of San Francisco, 5s, 1941	2 137 12
2,000	City of Seattle, 4¾s, 1957	1 995 00
2,000	City of Toronto, 5s, 1936	2 020 00
500	Oklahoma Gas & Electric Co, 6s, 1940	487 50
2,000	Port of New York Authority, 4½s, 1952	2 042.20
2,000	Port of New York Authority, 4¾s, 1958	2 065 40
2,000	Province of Alberta, 4½s, 1956	1 896 00
5,000	Province of Ontario, 4½s, 1933	4 925 70
2,000	Province of Ontario, 4½s, 1942	2 015 00
1,000	Province of Ontario, 5s, 1942	1,052.26
1,000	Township of Cheltenham, 4¾s, 1943	1 000 00
<u>\$60,500</u>	Total (Annual Yield, 4 57½%)	<u>\$61,496 71</u>

SCHEDULE No. II
 ENDOWMENT FUND, PRINCIPAL
 For the year ended December 31, 1931

Balance, January 1, 1931	\$ 8,400 00
Life Membership Fees collected during the year ended December 31, 1931		2,400 00
Transferred from General Fund in accordance with instructions of the Board of Regents		41,600 00
		<hr/>
Balance, December 31, 1931		\$52,400 00

SCHEDULE No. III
 GENERAL FUND, PRINCIPAL
 For the year ended December 31, 1931

Balance, January 1, 1931		\$79,938 86
Less		
Transfer to Endowment Fund in accordance with instructions of the Board of Regents	\$41,600 00	
Transfer to Endowment Fund of Initiation Fees of Life Members paid prior to January 1, 1931	500 00	42,100 00
	<hr/>	<hr/>
		\$37,838 86
Add		
Net Income for the Year Ended December 31, 1931 (See Schedule No. IV)		19,327 85
		<hr/>
Balance, December 31, 1931		\$57,166 71

SCHEDULE No. IV
 GENERAL FUND, INCOME AND EXPENSES
 For the Year ended December 31, 1931

INCOME

Annual Dues		\$27,160 10
Initiation Fees		18,365 00
Interest on Bank Deposits		1,351 76
Income from Endowment Fund	1,898 31	
Income from Bonds Owned	592 22	
	<hr/>	<hr/>
		2,490 53
Profit from sale of Keys, Pledges, Frames, etc		478 48
Receipts from 1929-30 Directory		5 85
Receipts from Annals of Clinical Medicine		11 00
		<hr/>
Total Income		\$49,862 81

EXPENSES

Fifteenth Annual Clinical Session		
Expenses		
Salaries	\$1,907 48	
Communications (Postage, Etc)	599 20	
Stationery and Office Supplies	129 82	
Printing	1,691 12	
Traveling Expenses	2,839 19	
Auditorium Charges (Rental and Services)	1,484 40	
Honorarium	50 00	
Entertainment	328 30	
Advertising	1,035 47	
Reporting	296 57	
Badges	399 01	
Ladies Committee	294 25	
Entertainment of Board of Regents and Guest Speakers	161 63	
Publicity	107 47	
Daily Bulletins	175.25	
Miscellaneous	442 23	\$11,941 39
	<hr/>	<hr/>
Forward	\$11,941 39	\$49,862 81

Forward		\$11,941 39		\$49,862 81
Deduct				
Banquet	313 25			
Exhibits	5,835 07			
Guest Fees	1,077 00	7,225 32		
Net Expenses			4,716 07	
Annals of Internal Medicine				
Expenses				
Salaries	5,637 41			
Communications (Postage, Telephone, Etc)	1,170 58			
Printing	18,800 46			
Traveling Expenses	50 00			
Miscellaneous	123 88	25,782 33		
Deduct				
Stationery and Office Supplies	15 59			
Subscriptions				
Volume I	\$45 03			
Volume II	33 09			
Volume III	51 40			
Volume IV	750 66			
Volume V	17,267 01	18,147 19		
Advertising				
Volume IV	\$2,329 07			
Volume V	1,600 19	3,929 26	22,092 04	
Net Expenses			3,690.29	
Executive Secretary's Office				
Expenses				
Salaries	9,494 02			
Communications (Postage, Telephone, Etc)	1,263 87			
Stationery and Office Supplies	761 97			
Printing	628 85			
Rent and Maintenance	3,136 61			
Traveling Expenses	1,807 92			
Annual Audit	150 00			
Premium on Surety Bond	20 00			
Press Clippings	105 65			
Miscellaneous	110 85		17,479 74	
Treasurer's Office				
Expenses				
Salaries	480 00			
Communications (Postage, Telephone, Etc)	45 00			
Stationery and Office Supplies	41 50			
Printing	3 95			
Traveling Expenses	176 54			
Annual Audit	50 00			
Premium on Surety Bond	100 00			
Miscellaneous	32 00		928 00	
Annals of Internal Medicine Distributed Free to Life Members			156 00	
1931-32 Directory (Cost of Production and Distribution)			3 202 38	
Depreciation on Furniture and Equipment			337 99	
Loss on Equipment Traded In			23 50	30 534 06
Net Income for the Year				<u>\$19 327.85</u>

President White presented the matter of the College having an exhibit at the World's Fair to be held in Chicago during 1933 under the title "A Century of Progress." A Committee from the Board of Regents had been invited by Dr. Eben J. Carey, in charge of Medical Section, Basic Science Division, Department of Exhibits, to a luncheon and an inspection tour of the plans for the exhibit. The plans are going forward under auspices which promise very active and possibly an extraordinarily interesting and profitable Exposition. A plan and diagram of the entire exhibit had been shown. In the scientific exhibit, it is proposed that a number of organizations should take part. The American Medical Association, the American College of Surgeons, and many scientific and medical institutions of this country and abroad, will have exhibits.

An invitation had been extended to the American College of Physicians to do likewise. There would be no charge to the institution for the exhibit space, but it would have to bear the expense of the preparation of the exhibit, its installation and supervision. Dr. Brown commented on a possible exhibit by the College, pointing out that an exhibit by the College, if entered, should be carefully worked up and well presented. Dr. Brown further pointed out that if the College undertakes the project, it probably would have to put it in the hands of a full-paid man, with power to act, secure information, appoint subcommittees and develop a scheme to be submitted to the College, perhaps, at their next meeting. He expressed the opinion that the College cannot well keep out of the exhibit, and that this Exposition is the most important thing we have ever had for mass education in the purposes, aims and development of Internal Medicine in the United States.

In further discussion, President White suggested the possibility of a moving picture exhibit which could be run serially to show the physician in the process of making the physical diagnosis and applying these various methods of diagnosis, along with the scientific knowledge that we have, to the human body. Dr. White went on to sketch other possibilities of practically carrying this out. The difficulty would be to concentrate on the things that would be most striking, most illustrative and most educational to the public. The exhibit, if entered, should be of the highest class and yet so devised that the man of the street could get some conception of its meaning, yet it should be of interest and value to the best informed as well.

Following thereafter was a considerable amount of discussion, engaged in freely by all members of the Board, with the result that the following resolution was presented and regularly carried:

RESOLVED, that a Committee shall be appointed to investigate the feasibility of the American College of Physicians entering an exhibit in the International Exposition, A Century of Progress, to be held in Chicago during 1933, that this Committee be informed that an appropriation of five thousand dollars, and not exceeding ten thousand dollars, would be made available for such an exhibit, if necessary, and if approved, and that this Committee shall report its findings, with plans, at the annual meeting of the College in San Francisco in April, 1932.

A further motion was regularly adopted, authorizing the President to appoint a Committee as above provided. President White appointed E. R. Loveland, Chairman, Dr. Clement R. Jones and Dr. James G. Carr.

The Secretary-General, in accordance with instructions from the Board of Regents, had drawn up the following resolutions, which were read by President White, and acted upon as later indicated:

"The Officers and Board of Regents of the American College of Physicians record with profound sorrow the death of their friend and late associate, Dr. Aldred Scott Warthin, whose death occurred on May 23, 1931.

"No history of the American College of Physicians will ever be complete without reference to Dr. Warthin's long and faithful service in the interest of the organization.

"Elected Second Vice President in 1923, he served in that capacity for two years. to be made First Vice President in 1925, a position which he occupied continuously until

the time of his death. As an Officer of the College, he brought to the counsel of the Board of Regents a keen mind which realized the needs of the College and ever sought to further its future development.

"As helpful as he was to the College in the capacity of an Officer, Dr Warthin's greatest contribution to the success of this organization was as Editor of the Annals of Internal Medicine. From the time that he assumed his editorial duties in the year 1923, the Annals progressed steadily in scientific value and importance. At the time of his death, through his able editorship and untiring labors, the Annals of Internal Medicine had become one of the outstanding medical journals in the English language, devoted to internal medicine and its allied branches.

"Dr Warthin was a great pathologist, an able teacher and a distinguished scientist, whose researches brought not only great credit to him, but added to the prestige of American medicine.

"To his associates on the Board of Regents, his loss is of a deeply personal nature. His wise counsel will be missed. In his death the American College of Physicians has lost a staunch supporter and a faithful and efficient Officer.

"Be it **RESOLVED**, therefore, that this resolution be spread upon the Minutes of the meeting of the Board of Regents of the American College of Physicians, and that a copy be sent to Dr Warthin's family to whom the Board of Regents express their deep and sincere sympathy."

Upon motion made by Dr Stewart, seconded by Dr C R Jones, and regularly carried, it was

RESOLVED, that the above resolution be adopted and published in the Annals.

The second resolution follows:

"The Officers and Board of Regents of the American College of Physicians record with profound sorrow the death of their late colleague, Dr Reynolds Webb Wilcox, on June 6, 1931.

"Dr Wilcox was one of the founders of the American College of Physicians. He had the distinction of being its first President. In this capacity he labored long and faithfully for the College. Throughout his life he retained his interest in the affairs of the College, and missed no opportunity to further its success.

"In recognition thereof be it **RESOLVED** that this resolution be spread upon the Minutes of the Board of Regents and that a copy be sent to the family of Dr Wilcox, to whom the Board of Regents wish to express their deep sympathy."

Upon motion by Dr Stewart, seconded by Dr C R Jones, and regularly carried, it was

RESOLVED, that the above resolution concerning Dr Wilcox be adopted and published in the Annals.

Dr Piersol pointed out that some action should be taken with reference to Dr Leonard M Murray, who had previously been a member of the Board of Regents for a long time.

On motion by Dr Bierring, seconded by Dr James Alex Miller, and unanimously carried, it was

RESOLVED, that the Secretary-General draw up a resolution to be dated as of December 20, 1931, concerning Dr Murray.

Authorization was granted by the Board of Regents for the two Committees on Credentials to hold a joint meeting three or four weeks before the San Francisco Clinical Session to prepare recommendations for elections to Fellowship and Associateship at the San Francisco meeting.

Adjournment

Attest E R LOWLAND
Executive Secretary

Acknowledgment is made of the receipt of gifts to the College Library of publications by Members, as follows

Dr Archie A Barron (Fellow), Charlotte, N C—I reprint

Dr C H Cocke (Fellow), Asheville, N C—2 reprints

Dr Carl V Vischer (Fellow) Philadelphia, Pa—I reprint

Dr A G Sullivan (Fellow), Hot Springs National Park, Ark, was elected President for 1932 of the Hot Springs-Garland County Medical Society at its annual meeting in December

In his official capacity as President of the U S Pharmacopoeial Convention, Dr Walter A Bastedo (Fellow), New York City, attended the Pharmacopoeial Conference on Vitamin Standards, January 15. After much discussion, the Conference, consisting of some 30 outstanding nutrition experts, adopted the standards arrived at by the International Conference called by the Health Organization of the League of Nations in London, June, 1931. For vitamin A the unit is 0.001 mg of carotene, for vitamin B, 10 mg of an absorption product of the antineuritic vitamin B, prepared according to the method of Seidell, for vitamin C, 0.1 cc of fresh lemon juice, and for vitamin D, 1 mg of the international standard solution of irradiated ergosterol

Dr William Engelbach (Fellow), New York City, delivered an address before the Genito-urinary section of the New York Academy on January 20, his subject being "Endocrine Factors Involved in the Development of the Genital System"

Dr A M Ornstein (Fellow), Philadelphia, Pa, has been elected President of the Philadelphia Neurological Society for 1932. On January 11, Dr Ornstein addressed the Men's Club of the Philadelphia Ethical Society on "Music in Medicine"

Dr C H Cocke (Fellow), Asheville, N C, is the 2nd Vice-President of the Southern Medical Association for 1932

Dr Leon T LeWald (Fellow), New York, gave an illustrated lecture on the "Evaluation of Roentgenology in Oto-Laryngology," before the recently combined section of Oto-Laryngology of the Academy of Medicine. Dr. LeWald especially stressed the value of iodized oil not only in the diagnosis, but also in the *treatment* of bronchiectasis

Dr Ralph Oakley Clock (Fellow), New York City, Adjunct Professor of Medicine at New York Polyclinic Medical School, presented a paper on "Bacteriologic Testing of Catgut Sutures" before the Section on Medical Bacteriology, Immunology and Comparative Pathology at the Thirty-third Annual Meeting of the Society of American Bacteriologists in Baltimore, Maryland, December 28-30, 1931

Dr Hyman I Goldstein (Associate), Camden, N J, had a paper on "Kinetocytes—A New Fourth Blood Element" in the January issue of the Delaware State Medical Journal

There is another paper by Dr Goldstein on "Kinetocytes" in the Medical Review of Reviews (N Y), February, 1932

At the Eleventh Annual Session of the Ohio Society of Clinical and Laboratory Diagnosis, held at Columbus, January 23, 1932, the following Fellows of the College contributed

Dr W M Sheppe, Wheeling, W Va, "Diabetic Neuritis with Paralysis,"

Dr Walter Simpson, Dayton, Ohio, "Significance of Agglutination Tests in Tularemia and Undulant Fever,"

Dr F C Hodges, Huntington, W Va, "Nephritis and Nephrosis"

Dr Neil Andrews (Fellow), Oshkosh Wis, addressed the Winnebago County Medical Society on January 15, at Mercy Hospital, on "The Heart, Past and Present"

Dr Grant O Favorite (Associate), Philadelphia, Pa, is the author of an article "Pathogen Selective Cultures in Chronic

Arthritis," which appeared in the January number of the Hahnemannian Monthly

Dr Albert F R Andresen (Fellow), Brooklyn, N Y, has recently contributed the following papers at meetings indicated

January 5, "Importance of Oral Examinations" before the Second District Dental Society, Brooklyn, N Y,

January 6, "Biliary Tract Diseases" before the Sullivan County (N Y) Medical Society,

January 7, "Pre- and Post-operative Care in Operation on the Stomach" before the Brooklyn Surgical Society and Brooklyn Society of Internal Medicine,

January 14, "Gastro-intestinal Allergy" before the Passaic County (N J) Medical Society,

January 29, "Relation between Oral Infections and Gastrointestinal Diseases" before the New York Gastroenterological Association

On February 15, Dr Andresen presided at a meeting of the Medical Association of the Greater City of New York, of which he is Chairman for Brooklyn. The speakers of the evening were Dr John B D'Albora (Fellow), Brooklyn, whose title was "The Treatment of Chronic Ulcerative Colitis," and Dr Martin E Rehfuess (Fellow), Philadelphia, whose title was "Medical Treatment of Gall Bladder Disease"

Dr Joseph C Doane (Fellow), Associate Professor of Medicine, University of Pennsylvania Graduate School of Medicine and Temple University Medical School, Philadelphia, addressed the Broome County (N Y) Medical Society at Binghamton, N Y, January 3, on "The Need for Cooperation Between the Doctor and the Nurse," on January 27, Dr Doane addressed the North End Branch of the Philadelphia County Medical Society on "Newer Methods in the Diagnosis and Treatment of Diseases of the End Arteries" and on February 4, Dr Doane addressed the Chester County (Pa) Medical Society at West Chester, on "The Future of the Community Hospital"

Dr William C Boeck (Fellow) was recently appointed Senior Attending Physician to the Los Angeles County General Hospital, and also was appointed to the Medical Faculty of the College of Medical Evangelists

On January 15, Dr Boeck read a paper on "Colitis" before the staff of the U S Naval Hospital at San Diego

The Section of Internal Medicine of the Los Angeles County Medical Association held a symposium on arthritis, February 3, 1932, with the following Los Angeles Fellows contributing

"Arthritis Due to Definite Organism,

Dr Roland S Cummings,

Discussion opened by Dr Roy Thomas,

Arthritis Due to Metabolic Disturbances,"

Dr S M Alt,

Discussion opened by Dr Paul B Roen,

Arthritis Deformans,

Dr John V Barrow,

Discussion opened by Dr William C Boeck

Dr John W Shuman (Fellow) and Dr John V Barrow (Fellow) are President and Secretary respectively of the aforementioned organization

Dr Samuel Weiss (Fellow) New York City, demonstrated before the New York Physician's Association, January 27 1932 a new Photographic Gastroscope. In addition, Dr Weiss showed for the first time a color film depicting the normal and abnormal state of the stomach

At the annual meeting of the Iowa Heart Association, held in Iowa City January 30 1932, the following Fellows of the College contributed

Dr Fred M Smith Iowa City, President's Address

Dr L R Woodward Mason City, VA Clinical Syndrome of Coronary Occlusion

Dr H W Rath Iowa City, Coronary Disease as Observed at the Univer

Years—Etiologic Types and Clinical Manifestations,"

Dr George B Crow Burlington, "The Prognostic Significance of Certain Signs in Chronic Heart Disease,"

Dr C D Mercer, West Union, "Diagnosis of Cardiac Arrhythmias at the Bedside,"

Dr Walter L Bierring, Des Moines, "The Lengthened Q Wave in Lead III,"

Dr Frank M Fuller, Keokuk, "Development of Valve Lesions Beginning in Childhood"

Dr Albert S Hyman (Fellow) Director of the Witkin Foundation for the Study and Prevention of Heart Disease, Beth

David Hospital, New York, N Y, was the guest speaker at the February 2 meeting of the Lackawanna County Medical Society held at Scranton, Pa. Dr Hyman's address was upon "The Irregularities of the Fetal Heart, A Phonocardiographic Demonstration"

Dr Hyman was also the guest speaker at the February 4 meeting of the Clinical Society of the Manhattan General Hospital, New York, N Y. His paper was upon "The Clinical Syndrome of Coronary Thrombosis," with a lantern slide demonstration. The paper was discussed by Dr John H Cudmore (Fellow), New York, N Y, Dr A E Parsonnet (Fellow), Newark, N J, and Dr A Yaguda (Fellow), Newark N J.

OBITUARY

DR CARL DONALD CHAPELL

Dr Carl Donald Chapell (Associate), Flint, Michigan, died January 10, 1932, at the Graduate Hospital, Philadelphia, of carcinoma.

Dr Chapell was born in Genesee County, Michigan, March 3, 1878. He graduated from the Michigan College of Medicine and Surgery in 1905 and soon after engaged in general practice in Flint. He became interested in Roentgenology and in 1927 limited his practice to this specialty. He was roentgenologist of Hurley Hospital from 1918 to 1929, and was responsible for the planning and equipment of the splendid X-ray and Physical Therapy Departments of that Hospital. At the time of his death, in addition to the direction of his own laboratory, he was roentgenologist at St Joseph's Hospital and the Woman's Hospital.

He was a member of the Genesee County Medical Society, of which he was president in 1924, a member of the Michigan State Medical Society, and a Fellow of the American Medical Association. He was a Fellow of the Radiological Society of North America, and an Associate of the American College of Physicians since 1922.

Dr Chapell was a very progressive physician and an untiring student in his specialty. Always friendly and helpful to his colleagues, his professional life was marked by devotion to the best tenets of medical tradition. He was an exemplary citizen whose unselfish service to the community will long be remembered. He is survived by his wife, a son and a daughter.

(Furnished by

JAMES D BRUCE, M.D., F.A.C.P.,
Governor for Michigan)

The Relation of The Intestinal Tract and Diet to the Treatment of Arthritis*

By RALPH PEMBERTON, M S , M D , F A C P , and E G PEIRCE, A B , M D ,
Philadelphia, Pa

PART ONE

THE RELATION OF THE INTESTINAL TRACT

THE problem of arthritis is the subject of an increasing amount of attention from the laboratory as well as the clinical standpoint. Because of this, various analyses of the problem which have fallen upon somewhat barren soil are now beginning to receive the consideration they deserve. This is true of so fundamental an aspect of the problem as the classification of Nichols and Richardson,¹ first published in 1909, but only now becoming widely known, and of certain fundamental orthopedic considerations, regarding "postural exercise", having to do with the mechanism and function of the body as a whole. It is also true of the therapeutic importance of a low calorie diet in arthritis and of the etiologic importance of the

gastrointestinal tract and the therapeutic consequences secondary thereto. This dietary phase of the question was developed by one of the present writers in 1912 and in a considerable number of subsequent publications, but has recently had additional emphasis at the hands of Fletcher.² This worker has adduced evidence from the x-ray standpoint relating to the intestinal tract which necessitates a further widening of our visual angle toward the disease.

That infection plays an important rôle in arthritis and many other conditions cannot be gainsaid. The present article constitutes in no sense an attempt to minimize its proven importance. The proper emphasis placed upon the infectious factors productive of arthritis and many other conditions has resulted, however, in undue domination of this concept and lack of inquiry as to how infection operates. In many instances the background upon which infectious processes become operative is laid long before these processes actually developed. Heredity, the constitutional makeup, the bodily configuration and other factors constitute prodromata which should excite active suspicion and should usually permit of prevent-

*From the Presbyterian Hospital and from the Orthopedic Hospital and Infirmary for Nervous Diseases, Philadelphia, Pa.

Received for publication, Oct 31, 1931

The work here reported is part of a study on Chronic Arthritis in collaboration with Dr Robert B Osgood of Boston. The expenses of the investigation were defrayed by contributions from various sources, including a number of patients.

ing onset of the disease. Neglect of these considerations cannot be condoned in those who attempt to treat arthritics. It is increasingly clear that factors quite other than infection may operate to induce and perpetuate the disease. It is no longer sufficient to state that a certain organism was found in a tooth or prostate and to administer the respective vaccine. Therapeutics which begin and end here, already constitute, in the eyes of many students of the subject, evidence of unfamiliarity with it. There can be no question in retrospect that hosts of arthritics have suffered because of first, extreme advocacy of the doctrine of focal infection; second, undue insistence upon, and even radicalism in, measures based on this concept, and third, because of the consequent exclusion of other measures, including even such generic agencies as those within the field of physical therapy. From a somewhat more philosophical standpoint, inquiry is now being made as to why infection arises in certain persons, why many such persons remain apparently well, why infection produces arthritis or other disease in some individuals, and how this result is brought about. It is not possible today to give a final answer to any of these questions. It is possible, however, to outline a number of factors which are definitely involved in these problems and to indicate certain therapeutic corollaries of importance attaching to them.

It is the purpose of the present article, therefore, to analyze further some of these factors, to adduce some corroboration of the work of others in relation to these factors, and to

make more available to arthritics, through their medical advisers, certain forms of therapy which in consequence are seen to deserve greater emphasis. In this brief article only the developing aspects of the matter can be touched upon and the reader is referred to previous publications¹ for fuller details.

It has been pointed out by one of the present writers that reduction of diet is followed by definite benefit in a certain proportion of arthritics. Subsequent clinical experience has further incriminated the food intake and also the gastrointestinal tract in the production of arthritis. In a long series of cases the writers and their associates have been impressed by the frequency with which anatomical, topographical and physiological abnormalities of the intestinal tract can be demonstrated in arthritics by x-ray studies.⁴ Others⁵ have made the same observation.

In a recent series of x-ray studies Fletcher² has shown, however, that under appropriate conditions of diet, these abnormal configurations of the bowel, chiefly the large bowel, return toward or to normal. This is so much the case that subjects of arthritis, characterized by bizarre configurations of the colon, may no longer be recognizable from x-rays taken in the convalescent period. The implication is plain, that this abnormal condition is probably of etiologic and pathologic importance and that therapeutic effort which does not include consideration of this phase of the problem may be either incomplete or irrelevant. It is of course appreciated that the range of normality in the configurations of

the intestinal tract is wide. Some apparently normal persons possess abnormal appearing colons. This point is wisely emphasized by radiographers. It would be improper, however, to fail to give adequate consideration to the matter on this ground alone and the analogy can well be cited of the hosts of apparently well persons who harbor abscessed teeth. It should also be pointed out that the apparent emphasis placed here upon the large bowel, to the relative neglect of the small bowel, is referable to the fact that the former only can be visualized and studied in any detail by x-ray processes under present conditions of technique. In point of fact, the stomach shares in principle the deviations of the intestinal tract as a whole, as the gall bladder apparently may also. This statement is made to disclaim the intention of confining attention to the large bowel, as is the vogue in some circles.

In the attempt to explain the general situation above outlined Fletcher has advanced the view that the enlargement and tortuosity of the bowel encountered, are referable to an unbalanced ration and avitaminosis. In substantiation of this view he cites the observations of Rowlands,⁶ and others⁷ upon experimental animals in which these abnormalities have been produced by diets high in carbohydrate and low in protein and vitamins. An interesting phase of the question arises from the fact that these animals are prone to infection in the course of this syndrome. Indeed, Melanby and Green,⁸ have reached the conclusion that inadequacy of vitamin A is one of the essential factors in the

development of low grade infections. Tisdall et al.⁹ state that "a vitamin intake below the amount required for normal metabolism may produce conditions of ill health other than those commonly recognized as deficiency diseases." An important factor in the development of the general syndrome under discussion is the interesting observation that animals which acquire abnormalities of the bowel of the kind mentioned, fail to do so, even upon an avitamin diet, if given a ration low in carbohydrate but containing an adequate protein content.

Fletcher observes that these several factors have been precisely those which, partly by intent and partly incidentally, have characterized the type of diet long advocated by one of the present writers in suitable cases of arthritis. It is therefore wholly conceivable that the vitamins may play an important contributory rôle in the development of this syndrome. The problem is complicated, however, and it is not possible as yet to dogmatize as to the relative importance of the three factors mentioned.

With the aim of attempting further analysis of the question twelve cases of chronic arthritis were studied and are here cited, in which the bowel showed more or less return toward normal, as described by Fletcher, following successful treatment of the arthritic subject. They definitely confirm Fletcher's conclusions in this respect. Some of the x-rays illustrating the changes in the configurations of the bowel are not as striking as are many of those reported by Fletcher, partly perhaps because the cases were not treated with this end in view and

partly because of differences in the time intervals or other factors. Some are even more graphic. It is noteworthy, however, that when the x-rays of the first nine cases were presented at random without any data to the writers, it was possible, by observing the x-ray of the bowel alone, to select in each instance the picture taken during ill-health and that taken during or after convalescence. Typical x-rays are appended.

The lines of treatment in these cases differed and it becomes desirable to attempt some preliminary evaluation of the relative influence of the therapeutic factors operative. If, for example, some cases of arthritis illustrate the phenomenon of the return of an enlarged and tortuous bowel toward normal, following removal of focal infection alone or the use of physical therapy, somewhat broader relationships might be entertained. The following cases do not all permit, as yet, of final conclusions but the etiologic and therapeutic importance of this phase of the problem justifies presentation of the data at hand.

CASE REPORTS

Case I Mrs. R. C-n-l-y, aged 32, had atrophic arthritis of twelve years duration following typhoid fever. She had no demonstrable foci and presented a typical intestinal form of case. She made a practically complete recovery on dietary control together with betterment of her gastrointestinal function and a broad program of rest, physical therapy and tonic medication. The colon was long and dilated, with marked cecal stasis. This picture yielded radically to treatment and an x-ray taken during convalescence showed a graphic contrast.

Case II Mrs. H--K, aged 55, hypertrophic arthritis, in menopause. She had no demonstrable foci but a long dilated colon with marked ptosis. This patient improved

clinically on a balanced regimen of rest, diet, improvement of intestinal function, massage, heat and postural exercises. The x-rays taken during ill-health and convalescence showed a marked contrast (See figures 1 and 2).

Case III Miss M. A-l-s-n, aged 65, hypertrophic arthritis. Typical intestinal case although she also had diseased tonsils. She made a complete recovery along purely dietetic lines in the presence of diseased tonsils. The gastrointestinal x-ray showed a long colon which improved markedly, coincidentally with convalescence.

Case IV Mr. W. A-st-g, aged 31, had severe atrophic arthritis of four years duration and wide spread involvement. The tonsils had been removed four years before. On admission he presented prostatitis and three abscessed teeth. The colon was long and dilated. The focal infections were removed or corrected, and a proper dietary was instituted, together with correction of his gastrointestinal function. A well balanced program of massage and tonic medication was established and the patient made a complete recovery. The contrasting x-ray pictures of the colon taken during ill-health and convalescence show marked differences.

Case V Miss T. G-l-n, aged 48, had widespread atrophic arthritis. She showed a marked clinical improvement on a restricted diet. The intestine showed a very marked and relatively rapid improvement coincident with her clinical improvement. Fuller details in Part 2, case XIII (See figures 3 and 4).

Case VI Mrs. Mc--m-r-a, aged 51, had hypertrophic arthritis of fifteen years duration. Her calf muscles were sore. Diseased tonsils were removed, a sinusitis was treated and several abscessed teeth were extracted. She showed a clinical improvement presumably following the above together with a regimen of regulated rest, modified diet, heat locally, general massage, and betterment of intestinal function. The bowel x-rays showed a distinct contrast.

Case VII Miss J. E-a-s, aged 55, hypertrophic arthritis with Heberden's nodes. The onset abruptly followed a tonsillectomy and appendectomy two years previously. This patient made a complete recovery upon

dietetic lines coupled with improvement of the gastrointestinal function. The x-rays of the colon taken during ill-health and convalescence showed a definite contrast.

Case VIII Mrs S H-n-y, aged 68, had hypertrophic arthritis with malum coxae senilis which caused her much pain. The muscles of her thigh were also very painful. Her diseased tonsils were treated locally. At the time of her admission her left thigh showed little rotation and flexion of her thigh caused the lumbar spine to descend. After a year of rest, diet, colonic irrigations, heat, massage and tonic medication the function of her left hip was much improved, her colon picture showed a corresponding improvement.

Case IX Mrs H St--t, aged 48, had atrophic arthritis. This patient presented a long redundant sigmoid together with marked dental infection. The case improved after removal of the teeth and then "hung

fire." Following correction of her diet and the marked intestinal stasis together with a full but well balanced program of physical therapy and tonic medication she made a complete recovery. The contrasting x-rays of the colon showed marked differences.

Case X Mrs G-st-1, aged 70, had hypertrophic arthritis. Her knees showed large overgrowth and some displacement of the tibial heads. She had diseased tonsils which were treated locally and two abscessed teeth which were removed. After this, the patient experienced a further improvement on a regulated life with periods of rest, local and general massage and a modified diet to which she was very faithful for a long time. At present, two years later, she remains in excellent condition. The x-rays of the bowel showed definite contrast.

Case XI Miss E A-h--d-ge, aged 53, had atrophic arthritis. This patient presented typical gastrointestinal invalidism



FIG 1

Case II Mrs I H--k

A case of hypertrophic arthritis with the colon showing ptoisis, lack of tone, reduplication, lack of haustra and regurgitation.

Case II Mrs I H--k

Appearance of the colon of the same patient following dietetic treatment. Note the improvement in tone, haustral markings and shape.

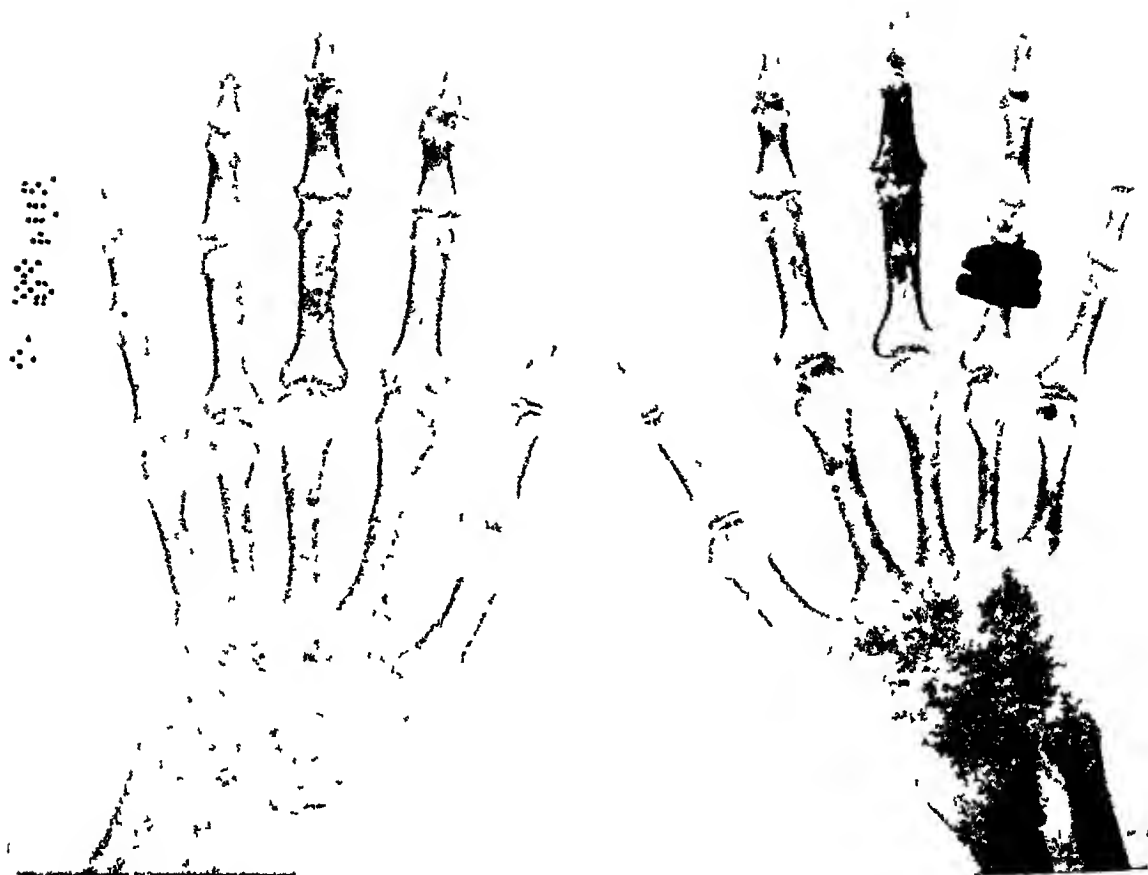


FIG 2 Case II Mrs I H--k Hypertrophic arthritis

and had lived for years on a carbohydrate diet avoiding "acids", meat, etc. The tonsils were buried and contained some pus but were not removed. She made a complete recovery along dietetic lines coupled with improvement of her gastrointestinal function. The x-ray picture of the colon showed a definite change after convalescence as compared with ill-health.

Case XII Mrs A M Gr--n, aged 57, had hypertrophic arthritis. This was purely a gastrointestinal type of case. The tonsils had been removed four years before without benefit. She made essentially a complete recovery along dietetic lines accompanied by correction of her intestinal function. The contrasting x-ray pictures of the colon taken during ill-health and convalescence show marked differences.

In few of the cases studied could any one single form of therapy be adhered to, to the exclusion of others.

It is possible, however, to evaluate with some confidence, the treatments used in each case. It is thus clear that the return of the bowel to or toward normal accompanies not only cases in which dietetics provided the dominant or exclusive therapy (cases III, V, and XI) but also cases in which the removal of focal infection (cases IV, VI and IX) and the exhibition of physiotherapy (cases II and X) played a conspicuous rôle.

It may be concluded from the data now at hand that the abnormal contour of the bowel encountered in arthritis is one consequence, probably a very frequent one, of arthritis in general, whatever its etiology. It thus follows, as elsewhere¹⁰ stressed, that once

established, the abnormal contour and, presumably abnormal function, of the bowel become an additional contributory or causative factor in perpetuating the disease. Arthritis thus may be originated by an infection, the removal of which in no way influences secondary consequences of this general nature. Furthermore, it is probable on theoretical grounds, and has been indicated on clinical grounds¹¹ that the above configurations of the intestinal tract, constitute, *de novo*, an original, exciting factor in the production of the disease. They may apparently be congenital and suggestions of this are not lacking in young children, as revealed by x-ray studies. These con-

figurations may also be acquired through pregnancy, faulty posture and the various factors that make for visceroptosis of which they often form a part. The relation of heredity and the consequent bodily makeup of the individual to this phase of the problem of arthritis becomes, therefore, of great significance and justifies the emphasis placed upon it by Osgood and his associates¹². It may be remarked that in these cases the gall bladder may be large, it may fail to empty adequately during conduction of the x-ray dye study and apparently shares with the gastrointestinal tract as a whole a condition of atony. The bile from such organs is by no means necessarily



FIG 3

Case V Miss T G-I-n

Atrophic arthritis, with the colon showing a voluminous sigmoid, an elongated transverse portion, and lack of haustral markings

Case V Miss T G-I-n

Colon of the same case of atrophic arthritis following dietary treatment. The ascending and transverse portions are narrowed and shortened and haustral markings appear where smooth surfaces formerly showed



FIG 4 Case V Miss T G-l-n Atrophic arthritis

infected By the same token, the stomach may be atonic and present hypochlorhydria

It is to be noted that both types of arthritis illustrated the change in the x-ray pictures of the bowel taken during ill-health and convalescence

The dispassionate view to be taken is that the etiology of arthritis at large

involves a cycle in which various factors are coordinated and that no one can be justifiably stressed, etiologically or therapeutically, to the exclusion of the rest The writers desire to emphasize that any concept of arthritis which fails to entertain consideration of these broad relationships constitutes a grave injustice toward arthritics as a group

PART TWO

RECENT DEVELOPMENTS IN THE USE OF DIET

The above studies afforded an extension of experience in the use of dietetics and justify some review or recapitulation of this field of therapy in the treatment of chronic arthritis Another justification for this is to be found in the increasing emphasis now

placed upon the two main types of arthritis and the consequent desirability of determining whether diet, or indeed any measure of therapy, has application more particularly or solely to either of these types

In view of what has been said in Part One regarding the configuration of the large bowel it becomes obvious

that the food intake and the intestinal function, using that term in its widest sense, are reciprocally concerned. Emphasis has properly been placed by Osgood, by the present writers and by others, upon adequate evacuation, especially by means of colonic irrigation, of the lower intestinal tract. Unduly popular with the laity, this has had considerable exploitation at the hands of certain enthusiasts. A wholly "mechanical" view of the problem, however, is not justifiable and the question is apparently not one of purgation alone, or of "washing out" putrefactive material or bacteria from the colon. As has elsewhere been stated,³ the institution of an appropriate dietary often affords a more fundamental approach to adjustment of the labors which the intestine is asked to perform. Much or most of that which is removed by irrigation is, precisely that which is taken in by mouth. Diet constitutes a difficult chapter, not to be entered upon lightly, but in some instances it constitutes also the *sine qua non* of successful therapy. This statement is not to be interpreted as justifying narrow emphasis upon this, or upon any other, aspect of treatment, because, as will be mentioned later, a coordinated and well-balanced attack is the great desideratum.

As already stated, experience with a recent series of cases has made it possible to determine definitely whether the beneficial influence of a diet is confined to either type, thus throwing some light upon the etiology of the two types. This question will be developed by first reciting the cases concerned.

ATROPHIC CASES

Case XIII Th-r-a Ga-l-n, aged 48, had atrophic arthritis of fourteen years duration, involving all the joints of her limbs. Diseased remnants of tonsils had been removed on the ward eight months before the present admission. She was costive and had a very long, reduplicated colon with ileocecal regurgitation. The patient was rested for a week in bed in the ward, on *ward diet*, before treatment was instituted. The ward diet is such as is given in most hospitals and is fairly high in carbohydrates. Objectively the patient became definitely worse during this week and her hands and knees became more swollen and painful. After forty-eight hours on a relative fast, to be described, her hands became less swollen and more wrinkled. A further improvement in hands, knees and other joints followed the regimen below.

First and second day—juice one orange, t.i.d., ample water

Third day—juice one orange, 1 cup coffee, 1 dram sugar

Fourth day—same as third, plus 8 ounces vegetable soup

Fifth day—same as fourth day plus 3 Uneeda biscuits

Sixth day—semi-liquid

Seventh and eighth days—1221 caloric diet

Ninth to thirty-eighth days—1465 calories

Thirty-ninth day—1800 calories

It will be noted that on bed rest plus a high carbohydrate and high caloric diet the patient became worse. On bed rest plus a low carbohydrate, low caloric diet she became promptly and definitely better. The improvement was beyond dispute and the patient volunteered similar evidence. (See Part One, case V.)

Case XIV Mrs. M. B-ne-t developed atrophic arthritis following, or soon after, an automobile accident six years prior to admission. She had typical lesions of atrophic arthritis in her hands. Injections of Coley's fluid had given her some help. The physical examination was negative except for a slight anemia. Infected tonsils and some abscessed teeth had been removed on a previous admission without benefit. During the first week of the present admission the patient was put to bed and allowed to eat the ward diet. She became decidedly worse.

as to swelling and pain in hands and knees, and was much discouraged. After three days on the orange juice regimen described under Ga-l-n (Part Two, case xiii) she showed improvement in her hands and felt better. The boggy swelling around the knuckles became much less noticeable and by the fifth day of the diet she could make a better fist. After five days on the orange juice diet she was given a day on semi-liquid diet, then for three days she was placed on 1403 calories and for the next six days on 1465 calories. She was discharged under observation very much improved as the result of diet alone, and has remained so eight months later. (See figure 5)

Case XIV Miss El-n-r As-br-ge, aged 52, came in complaining of swelling and stiffness in her left hand and wrist which she had had for six months. She had been rheumatic all her life and had suffered much from stomach trouble, as a result of which she had been living, on medical advice, largely on various forms of carbohydrate, as being the most digestible foodstuffs. She was costive and depressed. The physical examination showed the heart slightly enlarged with a slight systolic murmur transmitted to the axilla. The arthritis was of the atrophic type. Her tonsils were infected and she had one questionable tooth. For various reasons these foci were not removed. Gastrointestinal x-rays showed duodenal



FIG 5 Case XIV Mrs M B-ne-t A case of atrophic arthritis with improvement under dietetic treatment. The colon, by x-ray examination, showed marked changes coincidental with improvement.

stasis, a ptosed colon, the tip of the cecum fixed, bowel empty only after sixty-six hours. Atropine had helped her, but also made her constive. She presented the typical characteristics of the gastrointestinal invalid plus the syndrome of arthritis. Rest, colonic irrigation combined with colonic massage and a well balanced diet fairly low in carbohydrate and high in fat, with generous amounts of green vegetables and fresh fruits have been responsible for this patient's very striking recovery from her arthritic condition. Her disposition seems to have changed completely. She is now alert, cheerful and free from arthritis, adhering, though less rigidly, to the general principles of treatment.

Case XVI Mrs E. St-kd-le, aged 52, had atrophic arthritis of six years duration. This had followed diphtheria. The patient walked with a cane with great difficulty and pain,

because of flexion of her right knee to an angle of 45°. She had also a tender right wrist and some pain in the left wrist, shoulders and elbows. She was found on examination to have a systolic murmur, a rapid pulse and a blood pressure of 188/110. She had bilateral sinusitis, posterior ethmoiditis and remnants of tonsils had been left from tonsillectomy. She was treated locally and conservatively for her sinus condition without operation. This patient was very tired and depressed during the first part of her hospital stay. She exhibited improvement first following a day on a low calorie orange juice diet. Her knee gradually extended under a treatment that consisted of a diet of 1465 calories, part time bed rest, heat and cautious massage to the knee daily. The diet of 1465 calories which was used for two months was as follows:

	Calories Protein	Calories Fat	Calories Carbohydrates	Calories Total
1 1 egg, boiled	27.1	55.8		85
1 glass milk (hot)	29.8	81.8	41.6	157
30 grams bread	11.3	3.6	65.3	80
15 grams butter	6	118.6		119
250 grams orange	6.2	2.3	87.1	96
Total	75	262.1	194	535
2 Lettuce q.s.				
8 oz vegetable soup (strained)				
60 grams string beans	2	6.1	4.7	13
Mayonnaise, 1 tbsp	7.6	161.5	1.3	170
150 grams apple	18	4.2	66.4	72
1 glass milk	29.8	81.8	41.6	157
Total	41.2	253.6	114	412
3 100 grams chicken	131.6	40.9	8.6	181
50 grams spinach	4.3	19	6.7	28
50 grams beets	3.3	5	10.7	14
30 grams bread	11.3	3.6	65.3	80
15 grams butter	6	118.6		119
250 grams orange	6.2	2.3	87.1	96
Total	157.3	184.9	178.4	518
Summary				
	75	262	194	535
	41	254	114	412
	157	185	178	518
Total	273	701	486	1465

When the patient left the hospital she could walk with ease using a brace to protect the right knee from strain. She continued on the diet in modified form and later discarded the brace. She became entirely free from arthritis after following for many months the general principles laid down.

HYPERTROPHIC CASES

Case XVII Miss Mary A., aged 65, came in complaining of stiffness, aching and soreness in limbs and back, especially the knees, of five years duration. She had hypertrophic arthritis (figure 6). She gave a history of having severe eczema over a long period of time for which she had been treated by x-ray. The patient had formerly suffered from headaches. Her menopause had been attended by unpleasant manifestations. When first seen she had vertigo and was usually costive.

The physical examination showed a slight woman, reasonably well nourished, whose hands and knees gave evidence of hypertrophic arthritis. In all respects except those to be mentioned, her examination was not noteworthy, the cardiac dullness was slightly increased to the left, a systolic murmur was heard at the aortic cartilage and at the xyphoid, loudest at apex, with a leathery first sound, she had scattered râles in her chest, her liver border was palpable, in the upright position her abdomen was full and prominent. Her legs were both "bowed", especially the right, because of external slipping of the tibial head and her feet were flat with some pronation. Gall bladder x-ray dye studies showed a non-functioning gall bladder. Gastrointestinal x-ray studies showed a tortuous colon, sigmoid dilatation and ileocecal regurgitation. She had definitely diseased tonsils which, because of her age and cardiac condition, were not removed. A study of her dietary intake revealed that she ate an average of 1709 calories. She was given bed rest with general massage three times a week together with heat and massage as needed locally. She was put on 1540 calories consisting of a generous green vegetable ration, fresh fruit, butter, cream, meat and eggs, with relatively little carbohydrate. After thirteen days this was increased to 1700 which differed from

the diet the patient had chosen for herself in being lower in carbohydrate and higher in fat. After eight days on 1700 calories the patient was allowed 1958 calories which included 1 dram of Ol morrhuae, t i d. Five days later the diet was again reduced to 1540 calories. After two months in the hospital she left on 1700 calories. During her stay she made a decided improvement in her comfort in walking. She continued on her regimen outside with steady advance in the use of her limbs and is now well, two years later. *This patient never had colonic irrigations.* A picture of her colon taken after her convalescence shows that the colon has become less distended, shortened in certain parts, and that it shows the normal haustral markings more plainly.

Case XVIII Mrs. Ada G-l-t, aged 54, had hypertrophic arthritis. She was a slight, nervous woman without much reserve strength. She came in complaining of stiffness and pain in her hands, knees and back. She had suffered from arthritis for nine years. She complained of tingling of her fingers and shins. She had cramps in her arms when carrying things. Her tonsils were out. She had no demonstrable focus of infection. Her blood pressure was 130/85. Her physical examination revealed that she had a slight systolic murmur, but no cardiac enlargement. Her right kidney, or liver, or both, were palpable. She had some tenderness over the gall bladder region. Her left foot was somewhat pronated. She rocked her hips in walking though both femora flexed and rotated well. Her hands showed hypertrophic changes. X-ray of the gastrointestinal tract and colon picture by enema showed the colon to be of a contracted type. She showed no advance on a regimen of rest, massage, bakes and colonic irrigations. She gradually improved, however, on a low caloric diet, inaugurated by a four day period of orange juice, oz xii, q d. After four weeks on a restricted house diet this was repeated with the addition on the second day of 1 dram of sugar, and four fluid drams of whiskey to each portion of orange juice. This was followed by a diet of 1062 calories of such a character that it would be absorbed high in the intestine. This diet continued for two days, after which two Unceda

biscuits were added for two days. The house diet was then allowed for two days after which she was given for ten days a diet of 1500 calories, which was then raised to 1800 calories. The definite improvement in arthritic symptoms which the patient experienced at the end of her hospital stay was even more marked later after she had spent some time in a high dry altitude. She became able to lead an active life, riding horseback and entering into various pursuits, whereas when first seen she was a limping invalid. She was last seen "doing" a European art gallery on foot.

Case XIX Mrs B-r-ch, aged 52, had clear-cut hypertrophic arthritis. There were no focal infections. Her hands were involved to such an extent that she was unable to make a good fist. After being placed on the restricted diet described below, the patient became able in 6 days to flex her fingers markedly better.

First day—juice of one orange three times a day

Second day—as above plus 1 cup of clear coffee and 1 teaspoonful sugar

Third day—as above plus 8 oz of strained vegetable soup

Fourth day—as above

Fifth day—as above plus 3 Uneda biscuits

Sixth day—semi-liquid diet

Seventh day—1000 calories

Eighth to thirty-eighth day—1200 calories

After that—1465 calories

The patient showed further improvement subsequently and was quite well nine months later.

Observations made on certain of the cases studied have amplified other observations made in the army, previously reported,¹⁴ having to do with the application of dietetics in a radical manner involving underfeeding or starvation.

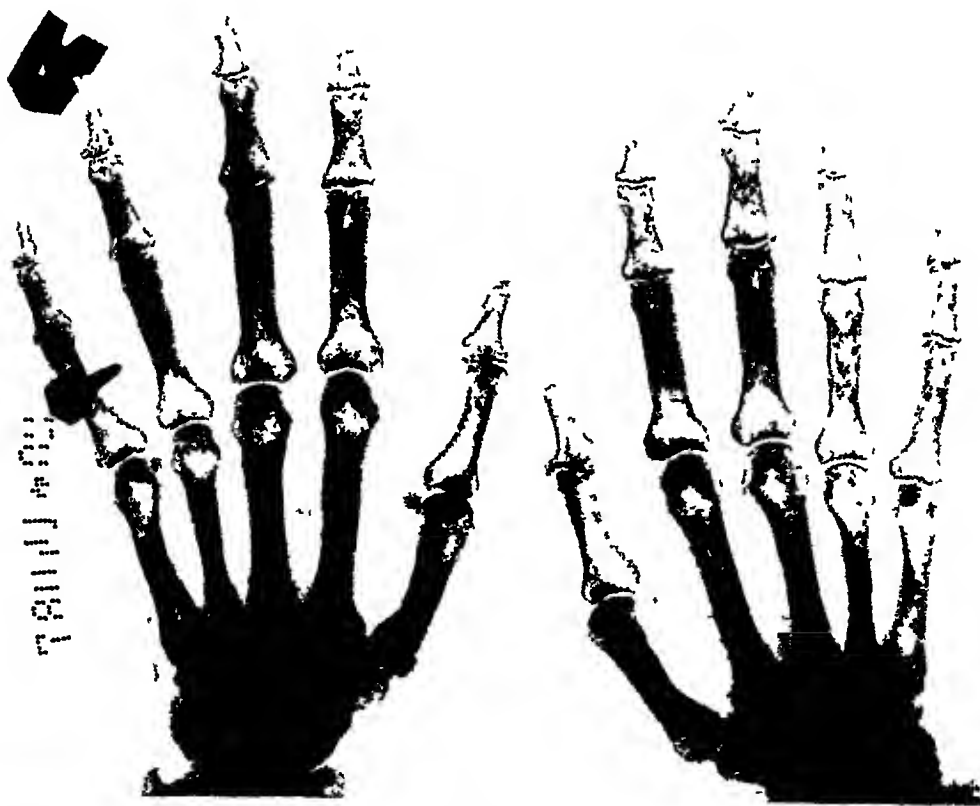


FIG 6 Case XVII Miss Mary A. Hypertrophic arthritis

It was observed in the army that under conditions approaching starvation a surprising degree of restoration of function sometimes took place in joints which had apparently been largely or wholly ankylosed. This ankylosis was obviously of fibrous nature but there apparently takes place at times under these circumstances a relatively rapid improvement of local physiological processes, including possibly absorption of detritus, which results in a betterment of function that may be of the first importance to the arthritic subject. Thus, in advanced cases of the Strumpell-Marie type of atrophic arthritis, the spondylitis ossificans ligamentosa of Knaggs, there is usually definite limitation of movement in hips, knees, wrists, etc. Within the bony limitations of such residual movement, however, thickening, contracture and adhesion of the joint structures may further lead to complete or nearly complete immobility. It would appear from the as yet limited number of observations available, that sharp curtailment of diet, approaching starvation, may bring about restoration of movement within the range of true joint movement remaining, to a degree which has not been regarded as possible. Some analogy to this is seen in animals suffering from experimental rachitis in which a short period of starvation inaugurates processes of regeneration in the bone notwithstanding the inevitably unfavorable prognosis as to life if the starvation be maintained.¹⁵ It is therefore valuable to cite the following two cases illustrative of this general state of affairs in arthritis.

Case XX M-r-g-t C-m-r, aged 24, had had atrophic arthritis for two years with pain and swelling in knees, ankles, hands and wrists. There was limitation of motion amounting nearly to ankylosis. All detectable foci were eliminated. She was in the hospital for two periods, the first for three months, during which time she made a limited improvement on physiotherapeutic treatment. On the next admission nearly a year later, she was put to bed and given a low caloric diet. During the regimen she was given no treatment other than rest and a low intake of food. The program was as follows:

First and second days—juice of one orange, t i d, ample water
 Third to eighth days inclusive—as above, plus 1 cup coffee, plus 2 drams of sugar.
 Ninth to eleventh day, inclusive—1078 calories
 Twelfth to fifteenth day inclusive—1196 calories.
 Sixteenth to twenty-first day inclusive—1278 calories
 Twenty-second to forty-fifth day inclusive—1480 calories

Six days after inauguration of the diet the patient had a larger range of motion in her wrists, upon measurement, and less tenderness in a swollen finger as observed by three persons. Subsequently the patient did well when able to adhere to the principles of treatment though the circumstances of her life made this difficult and sometimes impossible. She has recently married.

Case XXI C-l-a D-v-k-n, aged 27, had atrophic arthritis of thirteen years duration. Practically all joints were involved and the left hip was ankylosed, the right hip was becoming stiff and painful. The condition had been very stubborn and the patient experienced no improvement on Small's soluble antigen, on bakes, on massage or on colonic irrigation. She was given a sharp restriction of diet as follows:

First day—juice of one orange, t i d, ample water
 Second day—juice of two oranges, 2 drams sugar, t i d,
 Third day—juice of one orange, t i d, one cup of coffee, 2 drams of sugar, 8 ounces strained vegetable soup

Fourth day—as above, plus two Uneeda crackers

Fifth day—liquid ward diet

Sixth day to eighth day—house diet

Ninth day to twelfth day—1065 calories

Thirteenth to fourteenth day—house diet

Fifteenth to twenty-fifth day—1403 calories

By the fourth day there had occurred an increased range of motion in the right hip which had previously yielded to no other form of treatment. This betterment was maintained during the period of her stay in the hospital and subsequently (See also case 26 in reference 14.)

The recital of these last two cases is perhaps rather of academic than of therapeutic interest because the proportion of cases with fibrous ankylosis which would so respond is doubtless small and such cases must be carefully selected. Furthermore, the improper use of such measures might work great harm in some subjects of unstable equilibrium, especially in the presence of hidden infections, masked tuberculosis, etc.

A recital of the above series of nine cases shows clearly the undoubted influence of a restricted diet in the treatment of *properly selected* cases of arthritis. A number of cases are detailed in which no complicating form of therapy was brought to bear. The two main types of arthritis, atrophic and hypertrophic, each showed great improvement or full recovery as a result of the same measures. This implies some commonality of etiology and pathology and will be made the basis of another communication. A chief point at issue here is that to withhold the possible benefits of diet from either type, on the basis of *a priori* convictions relating to different treatment of the two types is often to manifest an injustice toward the

arthritic sufferer. *It is not recommended that cases of arthritis, en masse, be treated in this way because, as the writers have repeatedly emphasized, the successful therapy of arthritis consists in a properly coordinated use of the various measures available in this disease.*

It is particularly to be stressed that the measures approaching starvation detailed in these cases be not applied to arthritics in any wholesale way. The reader is specifically cautioned on this point. Underfeeding for any purpose is a two-edged tool which must be circumspectly used. The propriety of instituting dietetic treatment in arthritis must be determined independently in all cases. The factors concerned here have been discussed elsewhere at length, and the reader who contemplates applying these measures is urged to consult the references¹⁰ cited for the necessary details.

Bearing in mind the precautions emphasized, it is to be pointed out that the use of diet constitutes in many cases a foundation for other lines of therapy which alone would be futile. The state of affairs favorably influenced by a low dietary is probably present in many or most arthritics but the extent to which the influence of this measure can be brought to bear is strictly conditioned by the nature of the causes of the arthritis, the extent to which these causes can be removed, the nutrition of the patient, the existence of complications, the degree and chronicity of invalidism, the extent of the activities of the subject, and many other factors.

Finally, brief preliminary mention can be made of the fact that in a

series of four cases of arthritis representing both the atrophic and hypertrophic variety it has been possible to bring about sharp subsidence of the disease on the basis of a low caloric and low carbohydrate intake in which all vitamins were definitely excluded. Improvement was none the less rapid or marked, however, and the implication is plain that the presence of vitamins does not constitute the essential factor in the production of the benefit achieved. This observation does not exclude the possibility that the vitamin content of the diet importantly influences the development of and recovery from the syndrome discussed. The analogy of reparatory processes under conditions of starvation in rachitis induced in experimental animals by avitamin diets may have application here. At present, however, the indications are that the low caloric diet *per se* constitutes the essential factor in the experiments mentioned and that the rôle of the vitamins becomes influential in a somewhat more indirect manner and especially over long periods of time.

SUMMARY

Attention has previously been drawn to the frequency with which the syndrome of chronic arthritis, both atrophic and hypertrophic, is accompanied by enlargement and tortuosity of the large bowel. Corroboration is afforded, in the present contribution, of the work of Fletcher who has shown that, with institution of the type of diet previously described by one of the present writers, the bowel so distorted may return to or toward a normal contour. Apparently the condition de-

scribed may sometimes be congenital or it may be acquired. Once established in the course of cases of different primary etiology, the condition described may constitute an additional contributory factor in perpetuating the disease. Arthritis may thus be originated by an infection, the removal of which in no way influences secondary consequences of this nature. It is equally probable that the above configuration and ensuing dysfunction of the intestinal tract also constitute an originally exciting factor in the production of the disease.

Dietetic therapy affords the *sine qua non* of successful treatment in a large number of cases of arthritis. *Such therapy should be applied, however, to appropriate cases only, and on the basis of a familiarity with the principles concerned and with the limiting factors to which references are given in the text.*

In amplification of earlier work, it is shown that under conditions of undernutrition approaching starvation, not only may the active symptoms of the disease subside but there may be also, occasionally, an absorption of detritus or pathological exudate in or around joints, nearly or quite ankylosed, which reduces the amount of limitation to motion imposed by the existing fibrous contractures. In *suitably selected cases* the gain so achieved, though necessarily of small extent because of bony impingements and the like, may have great significance for the activities of the patient.

Finally, preliminary report is made of the fact that cases of both types of arthritis have experienced sharp im-

provement upon low calorie diets from which all vitamins were definitely excluded. While in no way negating the rôle of the vitamins in relation to the rheumatoid syndrome as a whole,

in the sense above discussed, it is clear that the reduced food intake and not the presence of vitamins primarily determined the immediate and sharp benefit observed.

REFERENCES

- ¹NICHOLS, E. H., and RICHARDSON, F. L. Arthritis deformans, *Jr Med Research*, 1909, *xxi*, 149-221
- ²FLETCHER, A. A., and GRAHAM, D. Large bowel in chronic arthritis, *Am Jr Med Sci*, 1930, *clxxxix*, 91-93
- ³PEMBERTON, R. Arthritis and rheumatoid conditions, their nature and treatment, 1930, Lea and Febiger, Philadelphia
- ⁴PEMBERTON, R. Loc Cit
- ⁵SNYDER, R. G., and FINEMAN, S. Clinical and roentgenologic study of high colonic irrigations as used in treatment of subacute and chronic arthritis, *Am Jr Roentgenol and Rad Therap*, 1927, *xvii*, 27-43
- ⁶ROWLANDS, M. J. Rheumatoid arthritis is it a deficiency disease? *Proc Roy Soc Med*, 1927, *xx*, 41-68
- ⁷MCCARRISON, R. Studies in deficiency diseases, 1921, H. Frowde, Hodder and Stoughton, London
- ⁸MELLANBY, E., and GREEN, H. N. Vitamin A as anti-infective agent, its use in treatment of puerperal septicæmia, preliminary communication, *Brit Med Jr*, 1929, *i*, 984-986
- ⁹TISDALL, F. F., DRAKE, T. G. H., and BROWN, A. New cereal mixture containing vitamins and mineral elements, *Am Jr Dis Child*, 1930, *xi*, 791-799
- ¹⁰PEMBERTON, R. Loc Cit
- ¹¹PEMBERTON, R. Loc Cit
- ¹²OSGOOD, R. B. Orthopedic aspects of chronic rheumatism or arthritis, *Jr Am Med Assoc*, 1930, *xcv*, 992-995
- ¹³PEMBERTON, R. Loc Cit
- ¹⁴PEMBERTON, R. Studies on arthritis in the army, based on four hundred cases roentgen ray evidences, clinical considerations, treatment, summary, conclusions, and clinical abstracts of cases studied, *Arch Int Med*, 1920, *xxv*, 351
- ¹⁵HAWK, P. B., and BERGMAN, O. Practical physiological chemistry, 1926, Blakiston's Son and Company, Philadelphia, 9th edition, p. 838
- ¹⁶PEMBERTON, R. Loc Cit

Toxic Granulocytopenia, Purpura Hemorrhagica and Aplastic Anemia Following the Arsphenamines*†

By ADOLPH B. LOVEMAN, A. B., M. D., *Ann Arbor, Michigan*

SENATOR⁷⁷ in 1888 reported four fatal cases of acute infectious pharyngitis. Unfortunately no bacteriological or hematological studies were made. Fourteen years later Brown⁷⁰ reported the first case of acute infectious pharyngitis with complete blood studies. The patient showed a marked leukopenia and on one occasion the polymorphonuclears were reduced to one per cent. From then until Schultz⁷⁵ reported his cases of agranulocytic angina, examples of an agranulocytic blood picture were described by Schwartz,⁷³ Turk,⁷² and Marchand.⁷⁴

As early as 1920, Moore and Foley⁷ reported agranulocytic blood pictures following the arsphenamines. Since then many cases have been added to the literature.

A voluminous literature is now available on agranulocytic angina, most of which has appeared within the past few years. One of the most complete and enlightening is that of Baldridge and Needles.⁵⁵ They are entirely justified in their condemnation of the term 'agranulocytic angina.' They

have shown very clearly and accurately that a-granulocytosis means, either an absence of a certain type of non-granular adult cell of myeloid origin (abnormal neutrophil), or else the term is derived from a-granulocyte-osis, in which case it would mean an absence of increase of granulocytes, that is a normal count. In modern medical nomenclature neither of the above interpretations is accepted. Since agranulocytic angina in the modern sense can exist without a true angina of the throat, this is added indication that Schultz's agranulocytic angina is an inadequate terminology. No doubt that which Schultz had in mind was a diminution to absence of granulocytes associated with a necrotic process in the throat, of unknown etiology, which terminated fatally. Since various factors can produce the above syndrome, which is preferably called granulocytopenia (Harkins⁵⁴), it is felt that wherever possible adjectives should indicate etiology, such as toxic or septic granulocytopenia. For the cases described by Schultz, any of a number of names are more adequate, namely, idiopathic granulocytopenia, idiopathic granulopenia, or if it is desired to emphasize the necrotic process in the throat, idiopathic granulocytopenic angina. At

*Studies and contributions of the Department of Dermatology and Syphilology of the University of Michigan Medical School, service of Dr. Udo J. Wile.

†Received for publication, July 28, 1931.

the present time evidence is against idiopathic granulocytopenic angina being a clinical entity and favors its being a syndrome caused by various etiological factors. Time alone will tell whether there is some hitherto unknown cause responsible for the condition described by Schultz.

Evans,⁵⁸ at Johns Hopkins, first reported a case of hemorrhage following arsphenamine, in 1916. At the time, however, he regarded this as a mere incidental finding. It remained for three French workers, Leredde,⁴⁸ Labbé and Langlois,³⁸ three years later, to bring this before the eyes of the medical profession.

Farley,⁹ in 1930, in reviewing the literature of all cases of bone marrow depression following the arsphenamines reviewed 39 cases and added 7, making a total of 46 cases. If, in our study cases have been uncovered which Farley failed to report, it is no fault of his, for such complications have been hidden under various titles and the articles have appeared in many languages, as well as in rather obscure magazines. It is entirely possible that certain cases have been unintentionally omitted from this report, but to our knowledge all cases available have been included. Many of the cases were unsuited for complete studies, but were used wherever possible in compiling our statistics.

A total of 64 cases of post-arsphenamine blood dyscrasias were found in the literature, with 31 deaths, a mortality of 48 per cent. Neoarsphenamine was the drug employed in 35 cases with 17 deaths, old arsphenamine was used in 10 cases with 5 deaths, sulpharsphenamine in 6

cases with 3 deaths, silver arsphenamine in 2 cases with one death, mixed arsphenamine therapy in 8 cases with 4 deaths. In addition, other arsphenamine preparations were used, the specific types of which were not stated, and in this group there were 3 cases with one death.

In the cases reviewed it was found that arsphenamine preparations attacked each element of the bone marrow, producing 30 cases of aplastic anemia with 18 deaths, 14 cases of purpura hemorrhagica with 5 deaths, and 15 cases of granulocytopenia with 6 deaths.

Under aplastic anemias have been grouped those cases in which there was a depression of all the elements composing the bone marrow, namely red blood cells, platelets, and polymorphonuclear leukocytes, whereas in the group of purpuras have been included only those cases in which the platelets were reduced. The term granulocytopenia has been reserved for those cases in which only the polymorphonuclear white cells were diminished. With the above classification in mind it is obvious that our cases of aplastic anemia include both cases of clinical purpura hemorrhagica and granulocytopenia. Our own case reports follow.

CASE REPORTS

Case I T. Y., age 53, white male. This patient entered the hospital on August 8, 1930, because of rapidly failing vision. He gave a history of a chancre eight years before with treatment consisting of four injections of neoarsphenamine with apparently no reactions.

Essential Physical Findings Eyes: Argall-Robertson pupils and primary optic atrophy in both eyes. Heart: Accentuation of both the aortic and pulmonary sec-

stream Roberts and Kracke⁷⁶ have shown conclusively that there is first a bone marrow depression which is followed in a few days by a hematogenous demonstration of granulocytopenia. Three to four days may elapse even after this is discovered before the patient complains of any clinical symptoms. In view of the above, it is quite probable that the blood count would have shown a mild reduction in polymorphonuclear cells before the onset of the patient's symptoms. The patient suffered a temporary exhaustion of his granulocytes with a temporary failure at production of them. This, no doubt, predisposed him to infection with the ordinary bacterial flora, producing a rather marked stomatitis, ulcerative pharyngitis, and tonsillitis.

This case cannot be called one of aplastic anemia because there is an increase in the platelets and only mild diminution of the red blood cells, no more than one would ordinarily expect from any acute infection. It actually fits in somewhere between a granulocytopenia and aplastic anemia and is an excellent illustration of how arsphenamine can affect various combinations of bone marrow elements. The symptoms, however, as well as the clinical findings, were probably caused by the failure of the bone marrow to produce polymorphonuclear cells in sufficient numbers, and therefore this case is considered one of toxic (arsphenamine) granulocytopenia. There is no adequate explanation for the increase in the monocytes except that it is a well known fact that when for any reason the polymorphonuclear cell is unable to respond to an infection it

is the monocyte that takes its place.

In spite of the negative cultures for Klebs-Löffler organisms, antitoxin was given, following which the patient commenced to improve. Whether the injection of antitoxin was coincidental with the crisis or whether it stimulated the exhausted bone marrow to further proliferation of granulocytes is impossible to state, although it is felt that the former is probably true.

Several cases have been reported in the literature paralleling the above. The one that is practically identical is that reported by Wilson⁵⁹. Dodd and Wilkinson,⁴¹ Moore and Foley,⁷ Foster,³⁷ Pouzin,³⁰ Gougerot, Barthélemy and Uhry²⁷ all report cases very similar to the author's.

Case II J. M., age 19, white female. This patient entered the Department of Dermatology and Syphilology on Feb. 20, 1931, with active secondary syphilis. She had had no previous antisyphilitic treatment. Physical examination revealed in addition to a follicular and maculo-papular syphilide, a palpable spleen. The rest of the physical examination was negative with the exception of some tenderness in the left lower quadrant caused from a pelvic inflammatory disease. Laboratory findings were negative on entrance.

Treatment	2-20-31 Intravenous injection No 1, arsphenamine, 3 gm
	Intramuscular injection No 1, bismuth salicylate, grams 2
	No reaction
	2-24-31 Intravenous injection No 2 arsphenamine 4 gm
	No reaction
	2-25-31 Intravenous injection No 3 arsphenamine 5 gm

Course in the Hospital Two days follow -

ing the last injection the patient became nauseated, vomited, and complained of pain in her left lower quadrant Her temperature was 102 degrees Six hours later the temperature rose to 104° A blood count revealed 7200 white blood cells and 70 per cent polymorphonuclear cells On March 1, 1931, the patient presented a toxic erythema She was placed on sodium thiosulphate daily, forcing of fluids, saline catharsis and alkalinization For the next six or seven days she ran a very stormy course, her temperature continued to climb, reaching as high as 107° Hypodermoclysis, protoclysis, and intravenous glucose were resorted to On March 8 rather marked improvement was noted, the edema of the face, which had appeared conjointly with the toxic erythema, began to disappear, as did also the rash The next day, however, the blood examination revealed a marked granulocytopenia, and the patient complained of sore gums Examination, however, revealed no ulcerations or hemorrhage Twenty-four hours later no polymorphonuclears could be demonstrated in the blood stream From March 10 to March 18 the patient received three transfusions of whole blood The appetite commenced to improve, as did the blood picture With the reappearance of the poly-

morphonuclears in the blood stream there was a disappearance of the sore gums There developed at this time a thrombophlebitis in the left arm and many subcutaneous perineal abscesses necessitating drainage Examination of the pus revealed numerous cocci and several newly-forming polymorphonuclear leukocytes On March 30 her condition had improved to such an extent that she was given her second injection of bismuth salicylate She made an uneventful recovery and was discharged on April 5, 1931

Summary The above case is that of a young girl who, the day following her third injection of old arsphenamine, developed a high fever associated with abdominal pain which was followed in a few days by a toxic erythema At the onset of this condition her blood picture was normal but there soon developed a picture of granulocytopenia associated with sore gums, but not accompanied by ulcerations or hemorrhage She ran a very stormy course, but after treatment consisting of daily injections of sodium thiosulphate, forcing of fluids, alkalinization, liver extract, local mouth antiseptics, and frequent small blood transfusions, she recovered sufficiently to be discharged 39 days after the onset of symptoms

Blood Findings in Case II

Date	R B C	W B C	Hgb	Plat	Diff	Remarks
2/20/31	5,070,000	9500	85%	Normal	Polymorpho-nuclears 54% Small lymphocytes 5% Large lymphocytes 32% Monocytes 8% Eosinophiles 1%	
2/26/31	4,370,000	7700	65%		Polymorpho-nuclears 77% Small lymphocytes 2% Large lymphocytes 7% Monocytes 7% Eosinophiles 5% Basophiles 2%	The day following last arsphenamine injection Fever 103 degrees Transferred to Gynecology because of pelvic pathology
2/27/31		15,000				

Blood Findings in Case II—*Continued*

Date	R B C	W B C	Hgb	Plat	Diff	Remarks
2/28/31	4,770,000	11,900	71%			Chill Fever 107° No malarial parasites found in smear
3/1/31						Sodium thiosulphate started
3/3/31		6,800	70%		Polymorpho-nuclears 70% Small lymphocytes 26% Large lymphocytes 2% Eosinophiles 2%	
3/9/31	4,420,000	2,000	73%		Polymorpho-nuclears 24% Small lymphocytes 45% Large lymphocytes 20% Eosinophiles 5% Unclassified 3%	Complains of sore gums
3/10/31	3,950,000	2,600	56%	Increased	Polymorpho-nuclears 0% Large lymphocytes 30% Small lymphocytes 14% Monocytes 45% Eosinophiles 10%	
3/11/31		3,300	76%		Polymorpho-nuclears 0% Small lymphocytes 18% Large lymphocytes 4% Monocytes 70% Eosinophiles 2%	1st transfusion of 300 cc of whole blood
3/12/31	4,860,000	2,350	73%		Polymorpho-nuclears 0% Small lymphocytes 56% Large lymphocytes 12% Monocytes 28% Eosinophiles 4%	
3/13/31						2nd transfusion 450 cc
3/14/31	4,190,000	3,150	65%		Polymorpho-nuclears 2% Small lymphocytes 44% Large lymphocytes 6% Monocytes 46% Eosinophiles 2%	

Blood Findings in Case II—Continued

Date	R B C	W B C	Hgb	Plat	Diff.	Remarks
3/18/31		5,400	84%		Polymorpho-nuclears 25% Small lymphocytes 30% Large lymphocytes 12% Monocytes 30% Eosinophiles 3%	3rd transfusion of 400 cc blood
3/20/31	5,200,000	7,100	84%		Polymorpho-nuclears 77% Small lymphocytes 16% Large lymphocytes 4% Monocytes 9% Eosinophiles 2% Basophiles 2%	Gums much better
3/29/31	4,540,000	7,150	78%	Increased	Polymorpho-nuclears 62% Small lymphocytes 16% Large lymphocytes 14% Monocytes 2% Eosinophiles 4% Basophiles 2%	
4/2/31	5,320,000	10,300	94%		Polymorpho-nuclears 65% Small lymphocytes 20% Large lymphocytes 7% Monocytes 6% Eosinophiles 1% Basophiles 1%	

Discussion of Case II Because of the mild anemia that developed as the condition progressed, this case, from the blood picture, is one of aplastic anemia. However, clinically it is considered one of toxic granulocytopenia for reasons similar to those in our first case. Prior to the onset of the patient's granulocytopenia, she suffered a not uncommon toxic reaction from arsphenamine, characterized by a toxic erythema, fever, vomiting and chills. At the onset the blood picture was normal, and at this time the patient did not complain of any sore gums, or

subcutaneous abscesses. However, as soon as she did, blood studies revealed a total absence of polymorphonuclear cells. Coincident with the return of the granulocytes to the blood stream, there was marked subjective and clinical improvement in the condition about the gums. The fact that granular white cells were found in the pus from the perineal abscesses may be considered an earlier sign for predicting improvement than the blood studies. Recovery in this case was no doubt materially aided by the intravenous injections of sodium thio-

sulphate and frequent small blood transfusions

Case III M D, female, aged 26 Entered the University Hospital March 31, 1931, because of severe swelling of the face, legs, sore mouth and sore throat This condition started 10 days before her admission and 24 hours after her fourth weekly injection of neoarsphenamine (0.75 gm, 0.9 gm, 0.9 gm, 0.9 gm) for primary syphilis She had run a fever of 101° to 103° F but had had no chills or jaundice The patient had been a known and treated diabetic for the past nine years Her mother is said to have pernicious anemia There was no history of any hemorrhagic tendency

Essential Physical Findings on Entrance The patient was dull and apathetic and gave every evidence of being acutely ill The entire mouth was inflamed and the gums were so tender that it was impossible to make a thorough oral examination A few superficial ulcerations were noted about the lips and tongue There was a blowing systolic murmur heard at the apex The abdomen was slightly distended The liver and spleen were not palpable The right ankle and tibial area showed pitting edema Vaginal examination and rectal examination revealed no ulcerations

Laboratory Findings on Entrance Blood W B C, 600, R B C, 4,100,000, Hgb, 80% (Salihi) Only one white cell was seen in 15 minutes examination of the stained smear Urine Trace of albumin, 3 plus sugar, 1 plus diacetic acid, 1 plus acetone Kalmi test Neg (repeatedly)

Course in the Hospital On admission the patient's temperature was 103°, pulse 120, and respirations 20 Her condition seemed to be quite serious and she was immediately given a transfusion of 500 cc of blood The following day she appeared somewhat better and was placed on a soft diabetic diet, without insulin She was given sodium perborate and warm saline mouth irrigations, alternating each hour From this time on she was given daily intravenous injections of sodium thiosulphate in one gram doses She was also given adenine sulphate in doses of 0.5

gram every other day, intravenously It was difficult to get the adenine sulphate into solution Normal 1/10 hydrochloric acid was finally necessary and the first dose of adenine was given by mouth, because of the fear of giving 1/10 normal hydrochloric acid intravenously It was discovered, however, that the solution could be satisfactorily buffered, and although this brought about a milky precipitate of the adenine, nevertheless given intravenously it caused no reaction She was given every other day small blood transfusions of 250 cc Daily white blood counts showed a small peak, the rise being on April 6, when a count of 1300 was reached The patient's diabetes was well controlled without insulin until April 7 when she showed 4 plus sugar and 3 to 4 plus diacetic acid in all specimens She was consequently placed on insulin, 16 units 3 times a day, which kept her sugar free The patient seemed to show definite improvement symptomatically The swelling and pain went down remarkably, she became brighter and the extreme soreness of her mouth diminished Re-examination of the mouth on several occasions showed large quarter-dollar sized sloughing areas, on the lateral pharyngeal wall of each side The patient continued to run an elevated temperature, as high as 104° There had been no startling changes in the white blood count There was however, symptomatic improvement until the morning of April 10, when the patient suddenly complained of severe generalized abdominal pain, associated with severe distension which could not be relieved by the ordinary measures Since some form of intestinal obstruction seemed obvious, she was seen in the Department of Surgery It was felt that in view of her other conditions a laparotomy was not warranted From this time her course was steadily downhill The skin assumed a definite icteric tint which increased markedly until death The conjunctivae which were clear previously also became icteric The white blood cell count dropped and on March 11 was 500 cells per c mm Her lung fields remained clear until the morning of that day when numerous coarse moist rales were heard in each lung base

ciated with a friction rub The patient died at 2 30 P M , March 11, 1931

Diagnosis at Autopsy "Agranulocytosis" Multiple necroses and early ulcers of tongue, pharyngeal tonsils, transverse colon and rectum Sub-acute adhesive peritonitis with acute fibrinous peritonitis superimposed Localized necrotizing perisplenitis Early pyemic abscesses in spleen. Acute hyperplastic mesenteric and retroperitoneal lymphadenitis Congested aplastic bone marrow. Encapsulated tubercles in bronchial lymph nodes Subendocardial fatty degenerative infiltration Acute passive congestion and parenchymatous degeneration of all organs

and hemoglobin, together with a marked leukopenia and absence of polymorphonuclears, make this case one of true granulocytopenia To our knowledge this is the first case of this type due to arsphenamine in which the nucleotide therapy described by Reznikoff³⁸ has been employed It is interesting to note again the occurrence of diphtheria-like organisms in cultures from the throat These findings are not new Baldridge and Needles⁵⁵ found similar organisms in cultures

Blood Studies					
Date	R B C	W B C	Hgb	Diff	Remarks
3-31-31	4,150,000	600	67%		Practically all white cells are lymphocytes, but so few that a differential is impossible
4- 1-31	5,270,000	750	80%		As above
4- 2-31		500			
4- 2-31		700			
4- 2-31		600			
4- 2-31		450			
4- 3-31	4,400,000	650	70%		32 lymphocytes and 2 polymorphonuclears on entire smear
4- 4-31		850			Lymphocytes predominate
4- 4-31		750			Lymphocytes predominate
4- 6-31		950			
4- 6-31		1150			
4- 6-31		1300			
4- 7-31		1200			
4- 8-31		900			
4- 8-31		650			
4- 8-31		850			
4- 9-31		750			Lymphocytes predominate
	5,060,000	900	93%		

Additional Laboratory Data Urine showed 2 to 3 plus sugar practically continually Highest blood sugar, 243 mg per 100 cc on March 31, 1931 Blood NPN 31.9 per 100 cc Blood chlorides 357 per 100 cc whole blood Culture from throat showed a bacillus morphologically typical of *B diphtheriae*

Discussion of Case III This case fits in classically with Schultz's description of agranulocytic angina except that here arsphenamine was no doubt the inciting etiological agent The apparently normal red blood count

from one of their cases These findings, however, are not believed to be of any great significance

There is a close similarity in this case to the first two The essential differences are that in this case there is more of a selective action on the granulocytes, as well as a longer period of depression than in cases I and II The bone marrow became so exhausted that it was unable to function With the disappearance of granulocytes from the blood stream and bone

marrow, the patient's immunity was greatly lowered and her resistance to infection was overcome. Thus there developed a stomatitis with extensive ulcerations and an ultimate fatal outcome. In short, as Roberts and Kracke⁷⁸ have shown, life is not compatible with an absence or granulocytes.

Our pathologist stated that he had never before seen such an extensive necrotizing process in a case of granulocytopenia as existed here, and no mention of such an extensive process was found in the review of the literature. Some pathologists, no doubt, would not consider this case one resulting from arsphenamine intoxication because no chemical evidence of arsenic was detected and the liver was not that of arsenical hepatitis. The present post-mortem chemical tests for arsenic were not considered sufficiently accurate to bear weight either way, and therefore were not employed. Perhaps the arsenic was stored exclusively in the bone marrow, thus accounting for the blood dyscrasia and absence of any arsenical hepatitis. Cases of bone marrow depression are too numerous in the literature for them to be mere accidental findings and thus there is no hesitancy in recording this as another one in spite of the failure to find certain classical signs of arsenical intoxication.

Case II. B. W., female, age 23. This patient entered the hospital December 19, 1929, complaining of weakness, bleeding from the gums and vagina, and marked fatigue. Six years before entrance she had had a primary syphilitic lesion. She was under constant treatment with neoarsphenamine and the heavy metals until three months before, at which time she entered a Detroit hospital. The last injection of neoarsphenamine was 10 months prior to the onset of her

symptoms. The exact number of injections is not known, but she stated that she had at least 50 injections of neoarsphenamine, together with bismuth, mercury and Bismarsen.

Essential Physical Findings. The patient was a pale undernourished woman who was mildly icteric. The tonsils were moderately enlarged. There was evidence of old hemorrhage at the gum margins and also a black line was present. The spleen was not felt. The liver was thought to be just palpable below the costal margin.

Blood Findings on Admission. RBC, 1,470,000, WBC, 2000, Hgb, 22%. Differential: polymorphonuclears, 33%, large lymphocytes, 26%, small lymphocytes, 34%, monocytes, 6%, eosinophiles, 1%.

Blood Kahn, negative. Urinalysis, negative.

A diagnosis of aplastic anemia following neoarsphenamine was made.

Course in the Hospital. Dec 23. The patient was started on adrenalin 0.4 cc. (This was increased daily until 0.7 cc. was given, after which she was maintained on this dose.) She was also placed on a high vitamin diet.

Dec 27. A transfusion of 500 cc. of citrated blood was given. Following this the temperature went to 102° and she complained of pain in the epigastrium.

Jan 3. Another transfusion of 500 cc. of blood given.

Jan 16. The patient has maintained her blood condition fairly well since the last transfusion. Bleeding from gums and nose noted.

Jan 23. Still bleeding from mucous membranes. The spleen was felt about 7 in. incl. below the costal margin.

Jan 29. Transfusion of 400 cc. of citrated blood. Temperature rose to 103°.

Feb 3. Ventriolum was started (10 grams daily).

Feb 25. Still bleeding occasionally. The condition is about the same.

March 6. Vaginal bleeding noted. Condition, however, improved.

March 9. Discharged.

Since the patient's discharge she has returned frequently for observation and treatment.

this has been impossible she has had blood counts taken and notified us of the results In this way it has been possible to follow her until September 2, 1930, at which time she

complained again of weakness, nervousness, and insomnia

Numerous blood studies were made, but only part of them are included below

Blood Findings in Case IV

Date	R B C	W B C	Hgb	Diff	Reticulocytes	Remarks
*10-11-29	1,280,000	2400	20%	Polymorphonuclears 43% Small monocytes 57% Large monocytes 0%		
*10-23-29	1,370,000	3050	30%	Polymorphonuclears 48% Small monocytes 45% Large monocytes 6%	6%	
12-20-29	1,470,000	2000	22%	Polymorphonuclears 33% Eosinophiles 1% Large lymphocytes 26% Small lymphocytes 34% Monocytes 6%		Platelets markedly diminished
12-24-29	1,200,000	3850	19%		1%	
12-27-29	1,280,000	3650	18%		1%	Transfused
12-28-29	1,970,000	3200	23%		1%	
1- 3-30	1,910,000	3150	23%		5%	Transfused
1- 4-30	2,680,000	3700	36%		8%	
1-29-30	1,460,000	2750	20%		15%	Transfused
1-30-30	2,050,000	3600	31%		21%	
2- 3-30	1,820,000	4150	30%		30%	Started ventriculin 10 gm daily
2-19-30	1,220,000	2900	27%		81%	
3- 6-30	1,330,000	4150	32%		6%	
3- 9-30						Discharged
4-10-30	2,250,000	5300	49%	Polymorphonuclears 66% Lymphocytes 44%		
5-14-30	3,500,000	5200	75%			
9- 2-30	2,616,000	5800	72%	Polymorphonuclears 54% Lymphocytes 44% Endothelial cells 2%		

*These two counts were made prior to entrance

nose and mouth Coagulin given Sodium thiosulphate, 1 gm, given intravenously

10-14-29 Condition unchanged Sodium thiosulphate given

10-15-29 No bleeding from the mouth until late in the evening

10-16-29 Emesis of dark, foul smelling fluid Weaker Nauseated Transfused with 650 cc

10-17-29 Small clots of blood expectorated Complains of severe headache Drowsy and sleeps at long intervals Temperature normal

10-18-29 Condition unchanged

10-19-29 Disoriented Found lying on the floor Pulse 48 Patient is cold Much weaker

10-20-29 Still bleeding from the gums Breath foul Incontinent Stuporous. Respirations labored Temperature 100, pulse 80, respirations 24 Respirations ceased at 11 25 A. M.

organs Fatty degenerative infiltration of liver Subepicardial fatty infiltration Active caseating tubercle in the bronchial lymph nodes Multiple caseating tubercles in the spleen and liver Hemorrhagic adenoma in the left lobe of the thyroid Syphilitic aortitis Atrophic scar on penis Old syphilis Bone marrow slightly hyperplastic Few megakaryocytes. Marrow smear shows diminution in red cell line and very few megakaryocytes Numerous normoblasts Very few megaloblasts

Summary In case V we have the case of a young man, who, after having received 13 injections of neoarsphenamine, developed signs of intoxication and intolerance to the drug evidenced by ecchymoses and petechiae He was given three more injections following which he became worse and commenced bleeding from the mucous membranes When admitted to the University

Blood Findings in Case V

Date	R B C	W B C	Hgb	Platelets	Differential	Remarks
10-10-29	2,330,000	11,500	46%	Absent	Polymorphonuclears 76% Lymphocytes 14% Monocytes 4% Eosinophiles 6%	Bleeding time, 18 minutes Clotting time normal
10-11-29						525 cc blood transfused
10-15-29	1,960,000	11,150	33%	Absent	Polymorphonuclears 66% Lymphocytes 24% Monocytes 6% Eosinophiles 3% Basophiles 1%	
10-17-29	2,830,000	14,500	50%	Occasional		Transfused 650 cc
10-18-29	3,420,000	13,300	55%	Rare		1 reticulo-cyte seen
10-19-29	2,850,000	18,450	51%			

Necropsy Findings Hemorrhagic diathesis of toxic origin (arsenic, mercury, bismuth?) Hemorrhagic necrotic encephalitis Multiple hemorrhages into the brain substance, meninges, subcutaneous tissue, gastric mucosa and subepicardial tissue, with hematoma in both renal pelvis Anemia Acute parenchymatous degeneration of all

Hospital he showed evidence of the above process Blood counts revealed a normal differential count, total absence of platelets, a moderate anemia, an increased bleeding time, and normal clotting time In spite of transfusions and sodium thiosulphate the patient died on his tenth day in the hospital

DISCUSSION OF CASE V

This is a typical example of purpura hemorrhagica, thus completing in this series of cases those illustrating the effect of the arsphenamines on each individual element of the bone marrow. This case cannot be called a toxic aplastic anemia in spite of the fact that there was a marked secondary type of anemia along with marked diminution of the platelets, because there was no apparent failure in the production of polymorphonuclear cells.

In the above case there were sufficient warning signs of intolerance to the drug to warrant discontinuing further therapy, and it is to be regretted that further arsphenamine was used after the appearance of these symptoms. Had immediate treatment been instituted following the first signs of intoxication the prognosis for recovery would no doubt have been greatly enhanced. Treatment, in spite of transfusions and sodium thiosulphate, proved inadequate, and the patient died, not of an aplasia of the bone marrow, nor as a result of infection, but rather because of hemorrhage. Necropsy substantiated this evidence when it showed a hyperplastic bone marrow with a diminution of the red cell line, together with multiple visceral hemorrhages. Death was no doubt due to a hemorrhagic encephalitis.

GENERAL DISCUSSIONS

Perhaps one of the most confusing and interesting problems to confront in these cases of post-arsphenamine blood dyscrasias is the etiological factor concerned. Some authors contend that it is the organic arsenic factor that is responsible whereas others feel

that it is the benzol radical, few take the attitude that both are responsible. Lawson, Jackson, and Cattana² in reporting 28 cases of inorganic arsenic poisoning have shown that inorganic arsenic may produce a marked diminution of polymorphonuclear leukocytes with a relative monocytosis. In their cases there was, in addition, a marked lowering of the platelet count and in several patients there were symptoms of gross intestinal bleeding as evidenced by bloody stools. In one case there was also a rather severe epistaxis. Wheelihan⁴² three years later reported a case of granulocytic aplasia of the bone marrow following injections of potassium arsenite in a child.

Organic arsenic obviously produces various types of bone marrow depression, as is shown by numerous cases including the author's.

Benzol is known to produce both a neutropenia accompanied by symptoms of marked sore throat, as shown by Rohner, Baldridge and Hansmann,¹ as well as purpura and aplastic anemia as shown by the same authors and also McCord,⁴⁷⁻⁴⁸ Sweeney,⁴⁹ and Selling.⁵

It appears then from such an analysis that no one drug is entirely responsible for all cases of bone marrow depression. Inorganic arsenic has been employed in medical therapeutics for centuries, but until Lawson, Jackson and Cattana² reported their cases in 1925, the literature failed to reveal any cases illustrating its toxic effect on the bone marrow. Prior to Faris's⁴ report in 1916 no cases were found in the literature illustrating the effect of organic arsenic on the bone marrow.

Sepsis, infection, irradiation, and chemicals are each known to produce depression of the bone marrow. There are other factors to be considered, however, for otherwise blood dyscrasias following the arsphenamines would occur more frequently. It is suggested that a predisposed, weakened, hematopoietic apparatus is probably of great importance as a secondary factor in every case of bone marrow depression. There is, however, still another factor to be considered as playing a rôle in the etiology of these diseases, and this is one heretofore entirely overlooked, namely, the syphilitic infection itself. There is at present no pathological evidence to indicate that these blood dyscrasias are due to actual invasion of the bone marrow by the spirochete, yet a syphilotoxic action should always be kept in mind as a possibility.

In addition to the etiological factors mentioned above might be mentioned drug idiosyncrasy, which is supported by the fact that one form of arsphenamine may be rather well tolerated, but when one shifts to another form (as from old arsphenamine to one of the neoarsphenamine preparations), symptoms of toxicity occur.

Inorganic arsenic, organic arsenic, and benzol, then, all play a share in producing bone marrow depression. Any drug that combines more than one of the above compounds, as do the arsphenamines, probably plays a greater rôle as an etiological agent than any of the drugs individually.

Among the organic arsenicals responsible for granulocytopenia, purpura, and aplastic anemia, neoarsphenamine is the greatest offender. In our clinic, however, this was not true,

both cases followed injections of old arsphenamine. It is possible that the explanation of this lies in the fact that in our clinic more of the old arsphenamine is employed than any of the other arsphenamine preparations.

Due to a certain lack of fundamental knowledge concerning the exact function of the bone marrow elements, it is hardly possible to make an accurate classification of diseases of the bone marrow with regard to etiological agents concerned. Certainly it is not within the scope of this paper to attempt such a thing in detail. However, for the sake of clarification, a rather simple classification which is in no way complete may be mentioned.

The arsphenamines may attack any or all of the elements of the bone marrow. If the platelets alone are depressed we get symptoms of purpura, and depending upon the degree of intoxication we get either simple purpura, purpura with hemorrhage, or, should other elements of the bone marrow be affected, purpura associated with aplastic anemia. Chemical toxicity is not the chief offender, for it is well known that purpura often results from other forms of toxicity, as well as from sepsis or bacterial infection. There might also be mentioned an idiopathic group.

The red blood cells when depressed are usually accompanied by a depression of platelets, polymorphonuclear leukocytes, or all three.

When the granulocytic element of the bone marrow alone is depressed, there results a true granulocytopenia. This likewise can be caused by chemicals, infections, irradiation, and sepsis. To this also must be added the idio-

pathic group. It is in this latter group only that the agranulocytic angina of Schultz should be placed.

If the circulating toxin, infectious products, or other etiological factors depress all three bone marrow elements, namely, platelets, red blood cells and polymorphonuclear leukocytes, a picture of aplastic anemia results.

Thus, with the above in mind, it is seen that in our cases reported the arsphenamines have acted on each of the individual elements concerned. To summarize, arsphenamine may depress either the red blood cells, platelets, polymorphonuclear cells, or any combination of these.

TREATMENT

In general treatment may be divided into two main divisions, namely, prophylactic and specific. The former is by far the more important. It was amazing in reviewing the literature to note the frequency with which treatment was continued after such gross clinical findings as bleeding from the gums, petechiae, membranous sore throat, and toxic erythema. It is much wiser to refrain entirely from the further use of arsphenamine after the appearance of such signs and symptoms and to continue therapy with one of the heavy metals. Occasionally, however, it is a safe procedure to allow the patient to have a rest period of three to six months following the employment of the arsphenamine preparation, and then start in again with smaller doses of a different arsphenamine preparation.

Moore and Keidel²² have shown that often a mild neutropenia exists

after such signs and symptoms as dermatitis exfoliativa, itching, stomatitis, and purpura, and they recommend complete blood studies before continuing any form of active therapy.

At present there is no specific treatment for any of the toxic reactions resulting from the arsphenamines, but regardless of other types of therapy employed, sodium thiosulphate, one gram daily intravenously, and frequent small blood transfusions, 250 to 300 cc three to four times a week, have been found of definite value in this clinic. There has been no opportunity in our clinic for employing immuno-transfusions, that is, blood from an individual who has recovered from the condition of which the patient is a victim. This, perhaps, offers possibilities and wherever convenient and safe should be employed.

CONCLUSIONS

1. Five cases of various types of bone marrow depression following the arsphenamines are reported and discussed.

2. The term 'agranulocytic angina' is inadequate and misleading. It is suggested that granulocytopenia is a better term.

3. Inorganic arsenic, organic arsenic and benzol may each depress any or all of the elements of the bone marrow.

4. In the blood dyscrasias following the arsphenamines, the arsenic and benzol radicals are probably both responsible.

5. A predisposed hemitopoietic weakness or insufficiency which in any case may be erythropoietic, thrombopoietic, granulocytopenic or any

combination of these, is perhaps an important secondary factor in the etiology of diseases of the bone marrow following arsphenamine administration

6. A syphilitic factor affecting the bone marrow is suggested as a possibility in the etiology of the blood dyscrasias in syphilitics

7 The most adequate treatment is prophylactic Sodium thiosulphate and frequent small blood transfusions offer the best means at present for combating the condition

For the privilege of presenting this paper and for many valuable suggestions, I am indebted to my chief, Dr Udo J Wile

For the privilege of presenting Cases III, IV, and V, I am indebted to Dr Cyrus C Sturgis of the Department of Internal Medicine

For many valuable suggestions, I am, likewise, indebted to Dr Raphael Isaacs of the Department of Internal Medicine

REFERENCES

- ¹ROHNER, F J , BALDRIDGE, C W , and HANSMANN, G H Chronic benzene poisoning, Arch Path and Lab Med, 1926, 1, 221
- ²LAWSON, G B , JACKSON, W P , and CATTANACH, G S Arsenic poisoning, Jr Am Med Assoc, 1925, lxxxv, 24
- ³ASKEY, J M Aplastic anemia due to benzol poisoning, Cal, and West Med, 1928, xxix, 262
- ⁴JENSEN, JULIUS Purpura hemorrhagica following neoarsphenamine, Minn Med, 1929, xii, 689
- ⁵KASTLIN, G J Agranulocytic angina, Am Jr Med Sci, 1927, clxxiii, 799
- ⁶O'LEARY, P A , and CONNER, H M Acute purpura hemorrhagica as complication in treatment of syphilis, Am Jr Syph, 1925, ix, 262
- ⁷MOORE, J E , and FOLEY, F E B Serious reactions from salvarsan and diarsenol brands of arsphenamine, unusual blood pictures, with report of a fatal case, Arch Dermat and Syph, 1920, 1, 25

- ⁸SELLING, L A preliminary report of some cases of purpura hemorrhagica due to benzol poisoning, Johns Hopkins Hosp Bull, 1910 xxi, 33
- ⁹FARLEY, D. L Depressed bone marrow function from arsphenamine, including type of so-called agranulocytosis, Am Jr Med Sci, 1930, clxxxix, 214
- ¹⁰KENNEDY, W R On occurrence of blood dyscrasia following administration of neoarsphenamine, Canad Med Assoc Jr, 1928, xix, 439
- ¹¹DALY, L W Acute purpura hemorrhagica following administration of sulpharsphenamine with recovery, U S Vet Bur Med Bull, 1930, vi, 62
- ¹²FRINBERG, S M Aplastic anemia following neoarsphenamine, Jr Am Med Assoc, 1922 lxxviii, 888
- ¹³WILLCOX, W H , and WEBSTER, JOHN The toxicology of salvarsan, dioxydiamido-arsenobenzol (salvarsan or kharsivan), Brit Med Jr, 1916, 1, 473
- ¹⁴VISWANATHAN, R Case of agranulocytic angina, Indian Med Gaz, 1930, lxxv, 328
- ¹⁵JONES, A B , and POTTER, B P Agranulocytic angina, Miss, Med Assoc, 1930, xxvii, 151
- ¹⁶LOWENBURG, H Neosalvarsan and leucocytes, New York Med Jr, 1919, cx, 326
- ¹⁷LERMAN, J Comparison of arsphenamine and catarrhal jaundice with special reference to blood picture, Am Jr Med Sci, 1929, clxxviii, 54
- ¹⁸TALLEY, J E , and GRIFFITH, G C Discussion of six cases of agranulocytosis, Med Clin North Am, 1930, xiii, 1079
- ¹⁹COMBES, F C , Jr Purpura hemorrhagica following sulpharsphenamine, report of case, Arch Dermat and Syph, 1927, xv, 194
- ²⁰FLORAND, A , et al Purpura under arsenical treatment, (abstract) Jr Am Med Assoc, 1922, lxxix, 1803
- ²¹APPEL, B Granulocytic purpuric hemorrhagic reaction after neoarsphenamine, Urol and Cutan Rev, 1930, xxxiv, 100
- ²²HELPS, J R , and WASHBURN, W A Toxic effects of arsenical compounds employed in treatment of syphilis in United States Navy, statistical study

- of results of 272,354 injected doses of neoarsphenamine and other compounds of arsenic, *Urol and Cutan Rev*, 1930, **xxiv**, 458 (Also, *U S Nav Med Bull*, 1930, **xxviii**, 659)
- ²³WEISKOTTEN, H G Action of benzol, *Jr Med Research*, 1927, **xxxvii**, 215
- ⁴²BUIST, T P Case of fatal hemorrhagic purpura following administration of sulfarsenol, *Jr Roy Army Med Corps*, 1925, **xliv**, 299
- ²⁷RABUT, R, and OURY, P Purpura from arsphenamine, *Presse méd*, 1922, **xxx**, 810
- ²⁶ANGLW-DAVIES, T Hemorrhagic purpura following therapeutic administration of neosalvarsan, *Brit Jr Dermat*, 1921, **xxxiii**, 264
- ²⁷GOUGEROT, H, BARTHELEMY, and UHRY, P Un cas d'agranuloeytose post-arsénobenzolique sans angine et sans hemorrhagies, *Bull Soc Franç de dermat et syph*, 1929, **xxvi**, 590
- ²⁸WEIL, P E, and ISCH-WALL Un cas d'anémie grave arsenobenzolique, *Bull et mem Soc Méd d hôp de Paris*, 1927, **li**, 319
- ²⁹WIDAL, F, and BERTRAND-FONTAINE Anémie aplastique grave associée a un syndrome purpurique et réalisant le tableau clinique d'une leucémie aiguë, survient a la suite d'injections de novarsenobenzol, *Bull et mem Soc med d hôp de Paris*, 1926, **l**, 980-985
- ³⁰KRUMBHAR, E B Leukemoid blood pictures in various clinical conditions, *Am Jr Med Sci*, 1926, **clxxii**, 519
- ³¹VEDFL, M, GIRAUD, M, and GIRAUD, M G Anémie pernicleuse aplastique post-novarsenobenzolique, avec hemorrhagies, purpura et atteinte hépatique, *Ann de dermat et syph*, 1923, **iv**, 712
- ³²NICOLAS, J, GATE, J, and LEBEUF, F Purpura aigue hemorrhagique post-novarsenobenzolique, *Ann de dermat et syph*, 1923, **iv**, 705-711
- ³³LAVBI, M, and LANGLOIS, S Purpura hemorrhagique aigu par intoxication arsenicale *Bull et mém Soc med d hôp de Paris*, 1919, **xliii**, 786
- ⁷⁴ESCHBACH, M H Contribution au rôle du novarsenobenzol dans les ictères chez les syphilitiques et dans les dyscrasies sanguines, *Bull et mém Soc méd d hôp de Paris*, 1919, **xliii**, 1120
- ³⁵JACQUELIN, A, CELICE, J, and LANGLOIS Sur un cas d'agranuloeytose post-arsenobenzolique, *Bull et mém Soc med d hôp de Paris*, 1929, **liii**, 8
- ³⁰LAIGNEL-LAVASTINE, M, LEVY, R, and DESOILLE, H Un cas mortel d'anémie aplastique hemorrhagique par intoxication benzenique professionnelle, *Bull et mem Soc méd d. hôp de Paris*, 1928, **lii**, 1264
- ³⁷FOSTER, J M, Jr Agranulocytic angina following administration of neoarsphenamine, report of case with recovery following use of sodium thiosulphate *Col Med*, 1930, **xxii**, 388
- ³⁸REZNIKOFF, PAUL Nucleotide therapy in agranulocytosis, *Jr Clin Invest*, 1930, **ix**, 381
- ³⁹POUZIN-MALLGUE (MME.) A propos d'un cas d'agranulocytose post-arsenobenzolique, *Bull et mem Soc med d hôp de Paris*, 1928, **lii**, 1786
- ⁴⁰SMITH, C M Severe bleeding and purpura following administration of neoarsphenamine, *Arch Dermat and Syph*, 1925, **xi**, 237
- ⁴¹DODD, K, and WILKINSON, S J Severe granulocytic aplasia of bone marrow, report of a case following arsphenamine treatment in congenital syphilis *Jr Am Med Assoc*, 1928, **xc**, 663
- ⁴²WHITTHAM, R Y Granulocytic aplasia of bone marrow following use of arsenic, *Am Jr Dis Child*, 1928, **xxxi**, 1032
- ⁴³LERLDDT, E Sur quelques accidents béniens, graves et mortels dus a l'arsénobenzol, *Rev gen de clin et de therap*, 1919, **xxviii**, 33
- ⁴⁴AUBERTIN, C Purpura, anémie aplastique hemorrhagique et agranulocytose post-arsenobenzoliques, *Monde med*, 1926, **xxxi**, 885
- ⁴⁵GIBSON, A G Action of adrenalin in aplastic anemia, *Lancet*, 1926, **ii**, 948
- ⁴⁶SMITH, A R Chronic benzol poisoning among women industrial workers, study of women exposed to benzol fumes in six factories, *Jr Indus Hyg*, 1928, **x**, 73
- ⁴⁷MCCORD C. P Present status of benzene (benzol) poisoning, *Jr Am Med Assoc*, 1929, **xem**, 280
- ⁴⁸MCCORD C. P Industrial benzol (ben-

- zene) poisoning, presence of immature red cells in blood stream Contributions to Med Sci, The Aldred Scott Warthin Ann Vol, 1927, 39
- ¹⁰SWENEY, J S Chronic aplastic anemia and symptomatic hemorrhagic purpura probably due to benzol poisoning, case report, Am Jr Med Sci, 1928, clxxv, 317
- ⁵⁰HAMILTON, ALICE Fifteen years of industrial toxicology, Contributions to Med Sci, The Aldred Scott Warthin Ann Vol, 1927, 231
- ⁵¹ROHNER, F J, BALDRIDGE, C W, and HANSMANN, G H Chronic benzene poisoning, Arch Path and Lab Med, 1926, 1, 221
- ⁵²MOORE, J E, and KEIDEL, A Stomatitis and aplastic anemia due to neoarsphenamine, Arch Dermat. and Syph, 1921, iv, 169
- ⁵³LINDSAY, J W, RICE, E C, and SELINGER, M A Purpura hemorrhagica following neoarsphenamine, South Med Jr, 1930, xxiii, 715
- ⁵⁴HARKINS, H N Granulocytopenia and agranulocytic angina with recovery Report of eight cases with four recoveries, Arch Int Med, 1931, xlvii, 408
- ⁵⁵BALDRIDGE, C W, and NEEDLES, R J Idiopathic neutropenia, Am Jr Med Sci, 1931, clxxx, 533
- ⁵⁶MILLS, E S Idiopathic aplastic anemia or aleukia hemorrhagica, Am Jr Med Sci, 1931, clxxx, 521
- ⁵⁷DAMESHEK, WM, and INGALL, M Agranulocytosis (malignant neutropenia), Am Jr Med Sci, 1931, clxxx, 502
- ⁵⁸EVANS, F A Transitional cell, Arch Int Med, 1916, xvii, 1
- ⁵⁹WILSON, C P Marked monocytosis accompanied by neutrophilic leukopenia following antisymphilitic treatment, Am Jr Med Sci, 1929, clxxvii, 88
- ⁶⁰CITRON, J, and HIRSCHFELD, H Hemorrhagic diathesis and aplastic anemia in treatment of syphilis, Med Klin, 1925, xxi, 805
- ⁶¹SCHULTZ, W, and JACOBOURTZ, L Agranulocytosis, Med Klin, 1925, xxi, 1642
- ⁶²THILL, O Akuter Morbus Werlhof nach Myosalvarsan Behandlung, Ztschr f klin Med, 1928, cix, 285
- ⁶³CALOMON, F Purpura haemorrhagica mit Hamaturie und letaler Lungenblutung nach Neosalvarsan Behandlung, Dermat Wchnschr, 1922 lxxv, 1197
- ⁶⁴UGRIUMOW, B, and IDELSOHN, J Ein Beitrag zur Kenntnis der aplastischen Anämie, Deutsch Arch f klin Med, 1927, clvii, 257
- ⁶⁵POGÁNY, E Fall einer Aleukie nach Salvarsan Behandlung, Ztschr f Hals-, Nasen- u Ohrenh, 1927-28, xviii, 383
- ⁶⁶FISHER, R L Case of agranulocytic angina successfully treated with immuno-transfusion, Jr Mich Med Soc, 1930, xxix, 435
- ⁶⁷MADERNA, C Porpora emorragica post-arsenobenzolica, Riforma med, 1927, xliii, 204
- ⁶⁸LESPINNE, and WIDOGHE Purpura after arsphenamine, Ann d mal vén, 1922, xvii, 241
- ⁶⁹WEIL, P E, and ISCH-WALL, P Hemorrhagic reaction to arsphenamine, Presse méd, 1925, xxxi, 657
- ⁷⁰BROWN, P K A fatal case of acute primary infectious pharyngitis with extreme leukopenia, Am Med, 1902, iii, 649
- ⁷¹BLUMER, GFO The agranulocytic blood picture in conditions other than angina, Jr Am Med Assoc, 1930, clxvix, 11
- ⁷²TURK, W. Septische Erkrankungen bei Verkummerung des granulocytensystems, Wien klin Wchnschr, 1907, xx, 157
- ⁷³SCHWARTZ, E Leucopenie, Wien klin Wchnschr, 1904, xvii, 806
- ⁷⁴MARCHAND, F Über ungewöhnlich starke Lymphocytose im Anschluss an Infektionen, Deutsch Arch f klin Med, 1913, cx, 359
- ⁷⁵SCHULTZ, W On different throat affections, Deutsch med Wchnschr, 1922, xlviii, 1495
- ⁷⁶ROBERTS, S R, and KRACKE, R R Agranulocytosis, report of case, Jr Am Med Assoc, 1930, xcv, 780
- ⁷⁷Taken from Brown ⁷⁰
- ⁷⁸ROBERTS, R, and KRACKE, R R Agranulocytosis its classification, with cases and comments, Ann Int Med, 1931 v, 40

(Appeared after this article was submitted for publication)

Ascending Paralysis Resulting from the Drinking of "Jamaica Ginger"; a Clinical Study of Fifty Cases*

By DELBERT H. WERDEN, M.D., *Los Angeles, Cal*

PARALYSIS resulting from the drinking of Jamaica ginger has recently presented itself in and around Los Angeles. Two hundred cases have been reported to date (March 1, 1931). This disease has been well studied and reported by various other observers since its first appearance one year ago in the Middle West and South. The cases occurring in the present so-called "epidemic" as encountered in this hospital† presented certain findings which differed from those of other authors as well as several new features which have not previously been described. In spite of a variable clinical history, the neurological findings are remarkably constant. Fifty cases have been studied in an attempt to learn more about the manifestations of the disease, and are herewith reported. An attempt has been made to emphasize the difference in the findings in my series from those already reported.

REVIEW OF THE LITERATURE

In reporting ten cases from the South, Bennett¹ considered the etiology obscure. All of his patients were corn-whisky drinkers and had taken

in addition Jamaica ginger. Of particular interest was a wide variation in the time of onset of the symptoms (3 to 42 days), and the presence of hyperactive patellar reflexes associated with absent plantar reflexes. In Bennett's opinion the disease was a type of Landry's paralysis. Harris² reported several cases occurring in an isolated village of 100 people. The findings in these cases were similar to those in Bennett's, and he suggested that the etiological factor was some recent change in the ingredients of the ginger, probably one of the higher alcohols.

Wilson³ reported a case in which the pupils were unequal, abdominal reflexes decreased but present and the Achilles' reflexes lost. He stressed the impairment of deep pain and vibration sense in the lower extremities. Although no visual disturbances were found in his case, Wilson referred to the cases of Thompson⁴ (1897) and Woods⁵ (1899) in which amblyopia resulted from ginger drinking. Goldfain⁶ emphasized the absence of Achilles' reflexes and complete loss of vibration sense in the toes with only partial loss in the legs. With the exception of the first, none of these findings was obtained in this series.

The pathology of the disease has been completely studied in the few

*Received for publication, July 20, 1931.

†Los Angeles County General Hospital.

fatal cases by Vonderahe,⁷ Jeter⁸ and Goodale and Humphreys.⁹ Vonderahe studied three fatal cases, one being uncomplicated by any other disease. The principal changes as he found them consisted of

- 1 Progressive changes in the anterior horn cells, characterized by swelling, chromatolysis and shrinking of the cell. Ventral root fibers showed degeneration of myelin sheath and axis cylinders;

- 2 Only slight involvement of the posterior horn cells,

- 3 Severe cellular degeneration in the hypoglossal and vagus nuclei and nucleus ambiguus.

Vonderahe felt that the toxin is non-infectious, first reaching the peripheral nerves, and from these traveling through the cord to the medulla. Jeter found an exudate of lymphocytes, a few polymorphonuclear cells, much engorgement of the vessels with red cells, and small deposits of fibrin in the cauda equina. His most constant finding was a fibrosis or thickening of the interstitial structure, especially the meninges of the cord, the peripheral nerves and the perineurium.

Goodale and Humphreys studied 62 patients with "Jamaica ginger paralysis" and reported the pathology in three cases. They often found fine red-brown granules in peripheral and perinuclear situations in the cytoplasm of the nerve cells. The nucleolus was frequently absent. Focal degeneration of myelin sheaths was observed only in isolated situations. The external popliteal nerve was most frequently affected, but no changes were found in any of the nerves above the gluteal fold.

ETIOLOGY

The etiology of the disease has been definitely worked out by Smith and Elvove¹⁰ who determined without doubt that triorthocresyl phosphate caused the degeneration of the myelin sheath, the axis cylinders and motor cells in the patients who were paralyzed in previous "epidemics." This compound is a stable combination of a phenol with a phosphoric acid ester, and was present in a concentration of about two per cent in the suspected "Jamaica ginger." Triorthocresyl phosphate has produced the identical clinical picture when given in small doses to rabbits, monkeys and calves.¹⁰ It has been suggested that the difference in susceptibility between rabbits and monkeys, and among different people was due to variations in degree of absorbability of the phosphate from the intestinal tract.

RELATION OF AMOUNT OF JAMAICA GINGER CONSUMED TO THE COURSE AND SEVERITY OF THE PARALYSIS

All of the patients here studied were of the lower and middle classes of people such as one finds in a general hospital. The average age was 49.6 years which was considerably higher than that given by Harris (between 20 and 40 years). Only three patients were women. A large majority were chronic users of alcohol. Accepting the statements of the patients, 5 were heavy drinkers, 25 were moderate drinkers, and 15 were light drinkers of alcohol. The remaining 5 patients were not chronic alcoholics and had taken no alcohol other than that in the Jamaica ginger. Most of these victims had been using alcohol either just before or with

the ginger, as follows 11 had been drinking heavily, 9 moderately, and 13 lightly Seventeen patients had taken no beverage other than the ginger

Jamaica ginger causing paralysis in the present epidemic was found to contain the same poison as was found previously by Smith and Elvove The ginger is sold in two or three ounce bottles and is taken principally for its high alcoholic content (80 per cent) When mixed with about four parts of water it is supposed to produce the usual "stimulating" effects of alcohol Some mix it with other forms of liquor and a few take it as a "sobering-up medicine" after an alcoholic debauch Two of the three women in the series had taken the ginger for dysmenorrhea Most of the patients were not habitual users of "Jake," having used it only one or two times before the onset of symptoms However, 13 patients were habitual ginger drinkers The amount of beverage consumed in these cases is indicated by the following

One patient	had taken	12	bottles per month	for 10 years
One patient	had taken	2	bottles per day	for 3 years
Three patients	had taken	2	bottles per day	for 6 months
One patient	had taken	4	bottles per week	for 6 months
One patient	had taken	1	bottles per day	for 1 month
One patient	had taken	2	bottles per month	for an indefinite time
One patient	had taken	6	bottles per week	for an indefinite time
One patient	had taken	3	bottles per week	for an indefinite time
One patient	had taken	2	bottles per week	for an indefinite time

In the study of these cases one was soon impressed by the great variation in the onset and course of the disease whereupon an attempt was made to learn the relation between

1 The amount and duration of the Jamaica ginger drinking,

2 The time between the drinking and the onset of the symptoms i.e. "latent period", and finally,

3 The extent and degree of the paralysis

THE AMOUNT AND DURATION OF DRINKING

The average number of two-ounce bottles ingested by the patients in this series was 5.5, and the average number of days in which they were consumed just prior to the onset of symptoms was 5.3, making the combined average about one bottle per day for five days This includes four cases in which only one bottle was taken, and eleven in which two were taken These figures are not given to show the amount of contaminated ginger necessary to cause the disease, but only to indicate the extent of the drinking in this series The assumption that patients absorb different amounts of the poison from the intestinal tract, as proposed by Smith and Elvove, makes it difficult to say how much of the phosphate is needed to cause the paralysis We know that with some patients as little as one two-ounce bot-

tle contains enough triorthocresyl phosphate to produce extensive degeneration in the peripheral nervous system

PERIOD OF ONSET

There have been different estimates regarding the number of days constituting the 'latent period' of the disease For patients having taken one

or two bottles in one or two days, the average time before the onset was 52 days, while the "latent period" for patients having taken from six to twenty bottles within seven days was 121 days. From these figures alone one would conclude that the more ginger taken the slower the onset, or that the patient works up a resistance to the poison, or perhaps that the cramps and weakness do not occur while the drinking is in progress. However, I am inclined to believe that the discrepancy is due to the fact that the patient who has been drinking for several days does not know just which of the suspected bottles of ginger contained the toxic element, and on what day he began taking the contaminated ginger. Therefore little reliance can be placed upon the history in this regard. This point is particularly well proven by the fact that in the series in which there was a large amount of ginger taken the average number of days from the drinking of the *last* bottle of Jamaica ginger to the onset of symptoms was 55 days. This last figure corresponds closely with the 52 days between the ingestion of only a *small* amount of poison and the onset of the first symptoms. However, here again one can only generalize in his conclusions, for in several cases from 22 to 29 days elapsed before the first symptoms appeared.

EXTENT OF PARALYSIS

It is also difficult to estimate the relation between the amount of ginger taken and the extent of the nervous system destruction, but an attempt is made to do so by comparing the number of patients with complete loss of

motor power and deep and superficial reflexes in a series of patients (10) who had consumed large amounts of ginger (6 to 20 bottles) with a similar series of patients (20) who had used only small amounts of ginger (1 to 3 bottles).

In those patients who had taken a much larger amount of poison, I have observed that

1 Motor power of the legs and the tendo Achilles' reflexes (L IV to S III), being already markedly impaired in nearly all cases having taken only small amounts of ginger, show no further loss.

2 Motor power of the quadriceps femoris, the patellar reflex (L II-IV) and the cremaster reflex (L I) are lost in twice as many cases.

3 Biceps reflex (C V, VI) is lost in 4 times as many cases.

4 Flexion of the wrist (C VI-TI) in 4 times as many cases.

These observations show that the degeneration is an ascending one, the height of which is somewhat proportional to the amount of triorthocresyl phosphate absorbed by the patient. Vonderahe⁷ came to the same conclusion after studying the cells in the motor nuclei of the medulla. One of our patients, a woman of 32 years, had all the findings of a degeneration which had ascended as high as the cervical cord. Abdominal and biceps reflexes were absent, and there was a complete loss of function of the hands and forearms. Fifteen days following her first symptom, she developed an aphonia and for three weeks could not speak above a whisper. Laryngoscopic examination revealed the vocal cords to be fixed in partial adduction.

Her pulse rate while lying quietly in bed varied from 60 to 120 per minute

SYMPTOMATOLOGY

Cramps, soreness and stiffness of the calves of the legs were the first symptoms in the majority (33) of the cases. About one-fourth of the patients also experienced weakness of the feet and legs at the same time, however, in most of the cases, weakness came on three days later. Sensory changes were conspicuously absent in all but three cases. The "dead" feeling of the feet described by many of the patients was found, on further questioning, to refer to loss of motion rather than to any sensory loss. Cramps of the calves of the legs occurred alone in fifteen cases, were accompanied by soreness in three cases and by stiffness in two cases. These cramps came on suddenly in the posterior crural muscles, sometimes while the patient was exercising, and were often severe enough to compel the patient to sink to the ground. The cramps were severe and painful, with a drawing sensation in the soleus, plantaris and gastrocnemius muscles. A few, whether intentionally or otherwise, have ascribed their misfortune to their occupation, and have tried to collect compensation.

Soreness in the calf muscles occurred alone in fifteen patients, was associated with stiffness in five cases and with cramps in three cases. This soreness most frequently came on after resting or on arising in the morning. All of these symptoms were moderately severe at first, increased in severity for twelve or eighteen hours, whereupon they subsided and in three days

were gone altogether. Occasionally after three or four days, and more often at night a few shooting pains developed, starting in the feet and traveling up into the hips. These lasted only a few hours and then vanished.

Weakness of the feet and legs appeared in an average of three days after the onset in most cases. The patient first noticed that his feet were beginning to "flop" and that he had difficulty in raising the feet from the floor. This weakness began in the dorsiflexors of the foot, next involved the plantarflexors, then progressed to the leg and thigh. Most observers have mentioned only the footdrop in this disease. It is my opinion that plantarflexion was impaired almost simultaneously and equally with dorsiflexion. Plantarflexion of the foot is a more passive movement than dorsiflexion, therefore impairment of this function is not noticed by the patient and is less conspicuous to the observer. I have found on physical examination both functions equally impaired. For a few days (two to nine) the weakness of the lower extremities increased, and finally the patient found his feet almost useless. He continued to hobble around with some assistance for three or four days more, then gave up and went to bed. From this point on for several months there was exceedingly little change in the patient's condition.

Weakness of the hands is an interesting phenomenon because of the consistency with which it came on after an average period of ten days from the onset of the initial symptoms. The length of this period was also found to be ten days by Smith and Elvøe,¹⁰ while Bennett¹ found that this weak-

ness appeared in three days in one-half of his cases. The patient first noticed impairment of extension and flexion of the wrists and fingers. He soon was unable to button his clothes, remove his glasses, or to grasp objects with any degree of strength or precision.

Another interesting observation was made in regard to the order in which the extremities first become involved. Thirty-two patients stated that their right hand was first to weaken. In only four cases was the left hand first involved, and one of these patients was left handed. In the lower extremities the onset was about symmetrical. That the lower extremities were first affected can easily be explained by the fact that the longer neurons in the lower extremities are more susceptible to degeneration. However, the only explanation I can offer for the right hand being involved first is that the most used extremity is more prone to weakening.

NEUROLOGIC FINDINGS

In many diseases of the nervous system the examination may be disposed of in favor of a good history. In Jamaica ginger paralysis, however, the histories are exceedingly variable in contrast to the striking similarity and consistency in the clinical findings. In most cases the condition could be diagnosed on the clinical findings alone. Two patients in the series applied for compensation for their illnesses. One said he had slipped and had fallen while carrying a load up an incline, following which he developed weakness, then paralysis. The other patient said he had been hit by a

swinging beam. Both denied having taken Jamaica ginger, but had typical findings of this type of paralysis.

If the patient is only slightly disabled and is walking around, he will have a "high stepping" gait, lifting his knees high in order that the dropped feet may clear the floor. The more disabled patient is found lying with legs extended, feet "dropped" and hands lying almost useless at his side. When the arms are raised the wrists assume a typical wrist drop. The feet appear sallow, and are cold and damp. The use of the muscles of the feet is almost entirely lost. The power of the anterior, posterior and lateral crural muscles is more or less symmetrically lost (96 per cent). The anterior femoral muscles (quadriceps and sartorius) become powerless in about half of all cases. In the upper extremities both flexors and extensors of the wrists are lost in 38 per cent of the patients, while in an additional 14 per cent the extensors are more involved than are the flexors. Where the weakness in the hands is only slight, adduction and flexion of the thumbs are the only movements impaired.

Sensation was remarkably normal in nearly all cases in this series, a feature which helps to distinguish Jamaica ginger paralysis from other types of peripheral neuritis. This finding has been so constant that I have come to believe it typical of this type of neuritis, even in view of the fact that Wilson³ and Goldfain⁶ state that there is a loss of deep pain sensation in the lower extremities, and a loss of vibration sense below the knees. In many of these cases the vibration sense was acute in the toes, causing

the patient considerable distress when touched with the tuning fork. In all except five cases both exteroceptive and proprioceptive sensation was entirely normal. This clinical observation was substantiated pathologically by Vonderahe⁷ who found only minor changes in the sensory columns and nuclei. Of the five patients who did have sensory changes, four had findings which strongly suggested that either syphilis or alcoholic neuritis was the cause of the impairment (See table II).

presents no explanation for the proprioceptive loss.

Irregularity of pupils was found in 28 cases, and inequality of pupils was found in 13 cases. In only nine of these two groups of patients were there positive Wassermann reactions. The light reflex was definitely slow or absent as compared to the reaction to convergence (accommodation) in 50 per cent of the cases in this series. Only six of these had positive Wassermann tests and two more gave a history of having had syphilis, but had

TABLE II
History and Findings of Patients Showing Sensory Changes

Case	History of Lues	Wass	Pupil		Sensation	
			Contour	Light Reaction	Extero-ceptive	Proprio-ceptive
I	Yes	Neg	Irreg	Absent	Absent	Absent
II	No	Neg	Reg	Present	Present	Absent
III	Yes	Pos	Irreg	Fair	Absent	Present
IV	Yes	Pos	Irreg	Absent	Present	Absent
V	No	Pos	Irreg	Fair	Present	Absent

Case I had taken one and a half bottles of ginger a day for six months, was considered a "moderate" alcoholic, and had taken a small amount of liquor before taking the "Jake." He therefore had cause for a true alcoholic neuritis resulting in both extero- and proprioceptive loss.

Cases IV and V were obviously tabetic, which could explain the proprioceptive loss. Case III had syphilis, irregular pupils, a slow pupillary reaction to light, and had taken two bottles of ginger a day for three years. As loss of exteroceptive sensation without a loss of proprioceptive sensation is rather unusual in both Jamaica ginger neuritis and syphilis, this case was probably one of alcoholic neuritis. Case II is the only one which

negative serology. The findings of pupillary changes in so many cases and in the absence of other disease, forces one to conclude that the same process affecting other nerves is also inhibiting the pupillary reflex.

Blurring of the nasal side of the disc margin was discovered in eleven patients. In two of these the discs were definitely "choked." Nielsen and Verity¹¹ observed Argyll-Robertson pupils and optic neuritis in a patient suffering with peripheral neuritis. On the other hand Harris² and Vonderahe⁷ found no changes in the discs or cranial nerves in any of their patients. The temporal halves of the discs were pale in twelve patients in this series. In two of these patients the discs were definitely atrophic.

probably due to syphilis. One patient who had optic atrophy had been thoroughly intoxicated before taking his ten bottles of ginger, suffered moderately severe retrobulbar soreness, and had a positive Wassermann test with absent pupillary light reflexes.

In general, the deep and superficial reflexes are a fair indication of the extent of the degeneration in the peripheral nerves and anterior horn cells of the cord. The tendo Achilles reflex is the first to be lost, and was absent in all cases except one in which only the left was elicited and another in which both Achilles' reflexes were present and normal. I believe the absence of this reflex is a constant and reliable sign in this disease as in other types of peripheral neuritis, even though in Vonderahe's cases⁷ the abdominal, Achilles' and patellar reflexes were all normal.

The cremasteric reflexes are next after the Achilles' reflex to be lost, being entirely absent in half of the cases and in nine more were lost on one side. In 21 cases in which the abdominal reflexes were entirely normal the cremaster reflexes were absent, or were absent on one side and considerably decreased on the other. Abdominal reflexes were completely absent in twelve cases, and in all but one of these the cremaster reflexes were also absent. This is to be regarded as a point of considerable significance, showing the level to which the degeneration has progressed.

The patellar reflexes were lost in eighteen cases. In only four cases were these reflexes increased, a marked contrast with the findings in Bennett's¹ cases of which one half had

hyperactive reflexes. In this series the fact that in eight cases the abdominal reflexes were still present while the patellars were absent shows how sharply the height of the ascending degeneration can be estimated, since the abdominals are supplied by the eighth to the twelfth dorsal segments, while the patellars are supplied by the third and the fourth lumbar segments.

The biceps reflexes were lost in only five cases, in two of these all other reflexes were lost, and in three only the abdominal reflexes remained. Of all patients in the series, one alone had no involvement whatever of the hands. It is assumed that the biceps reflex, being less often involved than those coming from lower down the cord, further indicates the extent of the degeneration and that the extent of the damage to the nervous system can easily be estimated by a careful examination of the various deep and superficial reflexes.

CONCLUSIONS

- 1 The disease can be definitely diagnosed on the physical findings alone. The history is often unreliable and is relatively of little importance.

- 2 The flexors of the extremities are affected almost equally with the extensors.

- 3 Sensation is seldom affected.

- 4 The lesion in Jamaica ginger paralysis is more than a neuritis. Clinical and pathological findings indicate that the process is an ascending degeneration, the extent of which is proportional to the amount of the chemical absorbed from the intestinal tract, and is manifest clinically by changes in the motor power of the extremities,

TABLE I
Showing greater loss of motor power and reflexes after taking larger doses of Jamaica ginger

No of Cases	Per Cent of Patients With Lost Function									
	Lost Power					Lost Reflexes				
	Leg		Thigh		Wrist		Lost Reflexes			Crem aster
	Flex- or	Extensor	Flex- or	Extensor	Flex- or	Extensor	Briceps	K J	Achilles	
10	100	90	60	90	60	70	20	60	100	60
20	95	95	35	95	5	30	5	25	95	35
	Total No Bottles		Ave No Bottles		No of days of Drinking					
	6 to 20		11.4		4.6					
	1 or 2		2.1		1.5					

and in the various deep and superficial reflexes

5 Although impairment of vision is not elicited subjectively, the disease frequently delays the pupillary light reflex, often produces irregularity of the pupils, and occasionally gives an optic neuritis

REFERENCES

- ¹BENNETT, C R A group of patients suffering from paralysis due to drinking Jamaica ginger, South Med Jr, 1930, xii, 371-375
- ²HARRIS, S Jr Jamaica ginger paralysis, (a peripheral neuritis), South Med Jr, 1930, xiii, 375-380
- ³WILSON, G Remarks on the so-called Jamaica ginger paralysis, report of a case, N Y State Jr Med, 1931, lvi, 70-72
- ⁴THOMPSON, A G Complete blindness due to acute poisoning from overuse of Jamaica ginger, recovery followed by toxic amblyopia of ordinary chronic form with eventual atrophy, Proc Phil Co Med Soc, 1897, xviii
- ⁵WOODS, H Jr Blindness following intoxicating use of Jamaica ginger, report of six cases, Ophth Rec, 1899, viii, No 2, 55-71
- ⁶GOLDFAIN, F Jamaica ginger multiple neuritis, Jr Oklahoma Med Assoc, 1930, xliii, 191-192
- ⁷VONDERAHE, A R Pathologic changes in paralysis caused by drinking Jamaica ginger, Arch Neurol and Psychiat, 1931, xvi, 29-33
- ⁸JETER, H Autopsy report of a single case of so-called yake paralysis Jr Am Med Assoc, 1930, xvi, 112-114
- ⁹GOODALE, R H, and HATHORN, M B Jamaica ginger paralysis, autopsy observations, Jr Am Med Assoc, 1931, xvi, 14-16
- ¹⁰SMITH, M I, LLOYD, E, and FRAZIER, W H Pharmacological and chemical studies of the cause of so-called ginger paralysis preliminary report, Pub Health Rep 1930, xl, 1703-1716
- ¹¹NIELSEN, J M, and VANDY, L E

- Argyll-Robertson pupils in polyneuritis Report of a case and theoretical deductions, *Ann Int. Med*, 1930, *iii*, 707-713
- ¹²RAW, N., BARENDT, F. H., and WARRINGTON, W. B. Epidemic arsenical poisoning amongst beer drinkers, *Brit. Med Jr*, 1901, *i*, 10-12
- ¹³REYNOLDS, E. S. A discussion on peripheral neuritis in beer drinkers; its precise causation and diagnosis, *Brit Med Jr*, 1901, *ii*, 1044-1049.
- ¹⁴TURLEY, L. A. Neuro-pathology found in cases with "jake" paralysis, *Jr. Oklahoma Med Assoc*, 1930, *xxiii*, 193-195
- ¹⁵NIELSEN, J. M., and STEGMAN, L. V. A case of nonsyphilitic pupillary inaction, *Arch. Neurol. and Psychiat*, 1926, *xvi*, 597-604

Reduction in the Incidence of Syphilis Possible

“**I**S syphilis in America on the increase or on the decline? Certainly we rarely see the rupioid and malignant types of syphilis that were formerly encountered. We believe that with education of the medical profession and with proper education of the laity as to the consequences of this disease that much good has and will continue to result. We would doubly emphasize the necessity of early diagnosis and of thorough treatment along with the more general and universal use of prophylaxis. With these forward steps and with compulsory examination of all applicants for marriage, syphilis in the next twenty-five to thirty years would truly take an enormous decline. Perhaps the day will actually come with syphilis, as with typhoid fever, that the disease will be so rare that the medical schools will have difficulty in getting material for teaching purposes. This millennium however is unfortunately not yet at hand.”

—(HAROLD N. COLE, M.D. Some observation on the treatment of syphilis, *Am Jr of Syphilis*, 1932, *xvi*, 21)

Peripheral Vascular Diseases

Treatment with Acetyl-choline Hydrochloride*

By W C WATERS, M D, *Atlanta, Georgia*

UNSATISFACTORY restoration of function so frequently follows surgical amputations for the gangrene of peripheral vascular diseases that interest in the treatment of such disturbances has been revived. Samuels¹ views the gangrene in these conditions as a self-limiting process and recommends conservatism until so much tissue has been destroyed that nonfunction appears to be inevitable.

Among palliative measures which have proved beneficial may be mentioned postural exercises,² the use of Ringer's solution by duodenal tube and by hypodermoclysis,³ and the intravenous administration of sodium citrate⁴ and sodium iodide solution.⁵

In 1926, Brown⁶ introduced the use of typhoid vaccine given intravenously to determine which cases were suitable for sympathetic ganglionectomy. He determined the "vasomotor index" after the temperature had been made to rise by the injection. This is calculated as follows: The difference between the rise in mouth temperature and the elevation in cutaneous temperature divided by the rise in the mouth temperature. An index of more than two indicates a large degree of vaso-

spasm in the disease, which ganglionectomy may be expected to relieve.

Following Brown's investigations, Allen and Smithwick⁷ gave small doses of the vaccine intravenously at spaced intervals to patients having far advanced vascular lesions in whom the operation was contra-indicated because of low vasomotor indices. They observed that reactions from injections were similar to those following periarterial sympathectomy, namely, relief of pain, elevation of the surface temperature, and improvement in the appearance of the local lesions. Of the twenty-five cases treated in this manner, eighteen were markedly benefited. The objection has been offered by Spurling⁸ that the severe constitutional reaction following the injection in these patients who are already debilitated, is undesirable.

The drug, acetyl-choline hydrochloride, was first used clinically by Villaret and Justin-Besançon⁹ in 1926 in a case of Raynaud's disease, in which the course of the disturbance was markedly alleviated. These investigators later described its action, the indication for its use and the methods of administration. It is a powerful vasodilator, this effect being produced by action on the arteries and arterioles. That the capillaries are not affected is

*Received for publication, July 17, 1931.

proved by the absence of flushing of the face following its administration¹⁰ while ophthalmoscopic examination shows dilatation of the central retinal artery to twice normal size¹¹

Acetyl-choline should be given subcutaneously or intramuscularly. Administered orally, it is without effect; while given intravenously, it is highly toxic and may prove fatal¹² The dosage varies from 50 to 100 mg, repeated at twelve to twenty-four hour

intervals. As improvement in the disturbance indicates, this may be reduced to once, twice or three times weekly According to Villaret and Justin-Besançon,¹⁰ no untoward reactions have followed two thousand personally administered injections and they report its action to be maintained with repeated use

They, further, have demonstrated a return of normal color and relief of pain in the affected parts from the use



FIG 1 Gangrene involving the large toe and medial surface of the foot There is a trophic ulcer at the base of the second and third toes

of acetyl-choline in Raynaud's disease, rest pain and intermittent claudication in thrombo-angitis obliterans was relieved, and improvement of trophic lesions and an increase in the oscillographic index was obtained. They mentioned no effect on the peripheral temperature following its administration.

Since the volume of blood flow through an extremity is measured by the rate of heat elimination,¹³ the estimation of the cutaneous temperature is of extreme importance in evaluating the effectiveness of treatment in peripheral disease. Diminution of surface temperature, particularly when associated with other signs of retarded blood flow, is characteristic of these disorders and as a rule improvement in the course of the disease is accompanied by elevation of the surface temperature in the affected parts.

In the cases herein reported, surface temperatures were taken after exposing the extremities to a room temperature of 70° F for thirty minutes. Then, the bulb of a mercury thermometer was placed between the bases

of the first and second toes which were strapped together with adhesive so that the skin was in contact with the entire surface of the bulb. Readings were made after the thermometer had been in place for three minutes. This method is accurate, simple and requires no expensive apparatus.

In one to three hours following the administration of acetyl-choline to these patients the cutaneous temperature was elevated from 2° to 5° C. The mouth temperature was not affected by the injection. This elevation lasted eighteen to twenty-four hours, at the end of which there occurred a drop to the original level. Accompanying this reaction the patients experienced a sense of warmth and relief of pain in the affected extremities. The administration of the drug daily, or every other day, over a period of time produced an increase of the surface temperature to a constantly higher level, complete relief of pain and eventually disappearance of the gangrene. Since the surface temperature of an extremity is an index to the

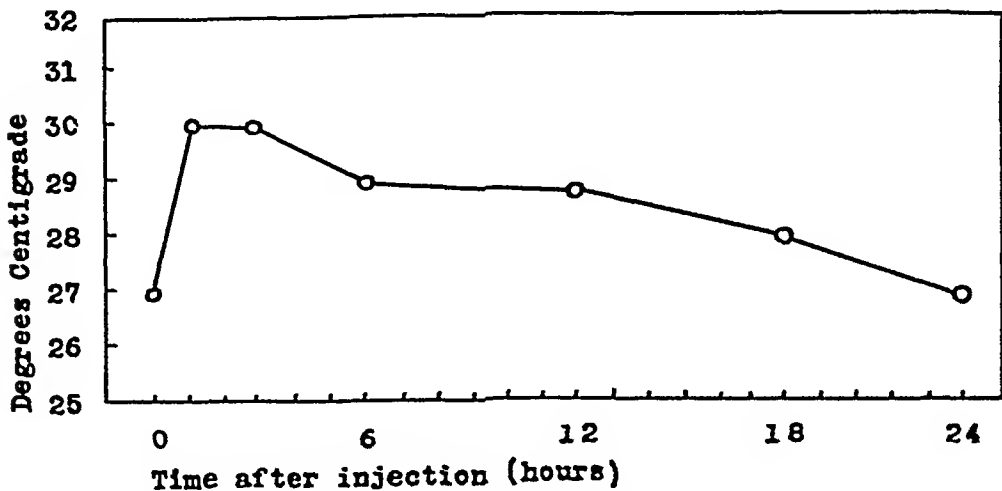


CHART 1 Surface temperature readings in case I after the injection of 10% of acetyl-choline.

adequacy of its blood supply, a reduction in this reading after acetyl-choline has been discontinued should be accepted as an indication that the drug is still required

The disadvantages of foreign protein administration are not encountered with the use of acetyl-choline. These are (1) the lack of a uniform and constant effect, (2) the possibility of vascular occlusion during the chill, (3) the necessity for hospitalization, and (4) the undesirability of the induction of fever for debilitated patients

The following cases are selected to

illustrate the immediate rise of the peripheral temperature following an injection of acetyl-choline to those having trophic lesions resulting from obliterative vascular diseases and to demonstrate the effectiveness of the use of the drug in the treatment of these disorders

CASE REPORTS

Case I A woman, aged 46 years, was referred for treatment because of diabetic iritis. In addition to polyuria, excessive thirst and voracious appetite, she complained of pain in the feet radiating into the calves of the legs. Since there was diminution of all types of sensation in the legs, and pul-

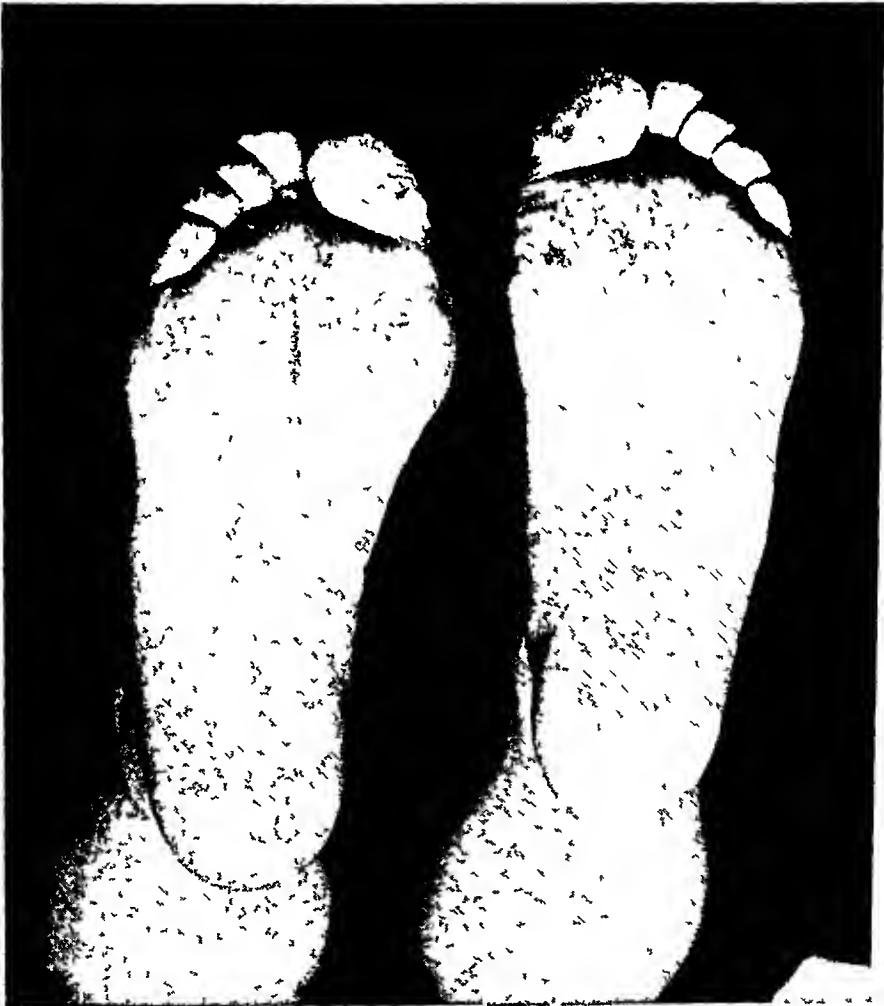


FIG 2 Healing of gangrene and the ulcer three months later following the use of acetyl-choline

sations in the dorsalis pedis and anterior tibial arteries appeared adequate, it was thought at the time that the pain complained of was due to diabetic neuritis

Physical examination disclosed no abnormalities. The fasting blood sugar estimate was 250 mg per 100 c c and the urine contained a large amount of sugar

Following restriction of diet and the administration of 20 units of insulin daily, the urinary sugar disappeared and the fasting blood sugar returned to a normal level

Nevertheless, two months later she developed an ulcerative lesion at the base of the first toe of the right foot. Shortly thereafter, gangrenous areas appeared at the bases of the second and third toes and over the plantar surface of the large toe (figure 1). In spite of the presence of apparently normal pulsations in the peripheral arteries, there was blanching of the feet with elevation and rubor with dependency. The surface temperature of the right foot was 27° and of the left 28° C

In spite of rest in bed and the use of local heat, the gangrene appeared unimproved at the end of two weeks. One hour following the intramuscular injection of 100 mg of acetyl-choline the cutaneous temperature in the feet was increased to 30° C. This elevation lasted twelve hours, at the end of which the temperature gradually

dropped to the previous level (chart 1). The administration of the drug daily during the next two weeks resulted in marked improvement in the local lesions. A continuation of the injections twice weekly for the next three months produced complete healing of ulcerations (figure 2), disappearance of postural color changes and elevation of the surface temperature to a level constantly above 29° C (chart 2)

Case II A woman, 38 years of age, complained of small painful ulcerative lesions symmetrically distributed over the tips of the first, second and third toes of the feet. These had appeared five days previously. For years she had suffered with cold feet, more pronounced in the winter

Digital examination revealed normal pulsations in the popliteal arteries but none were felt in the dorsalis pedis and anterior tibial vessels. The cutaneous temperature of the feet was 24° C and postural color changes were marked

The gangrene persisted in spite of the use of heat and rest in bed for a week

One and one-half hours after the intramuscular administration of 100 mg of acetyl-choline, the surface temperature of the feet increased to 29° C (chart 3), and pulsations returned in the peripheral arteries. This reaction lasted for eighteen hours. The use of the drug in this dosage every other

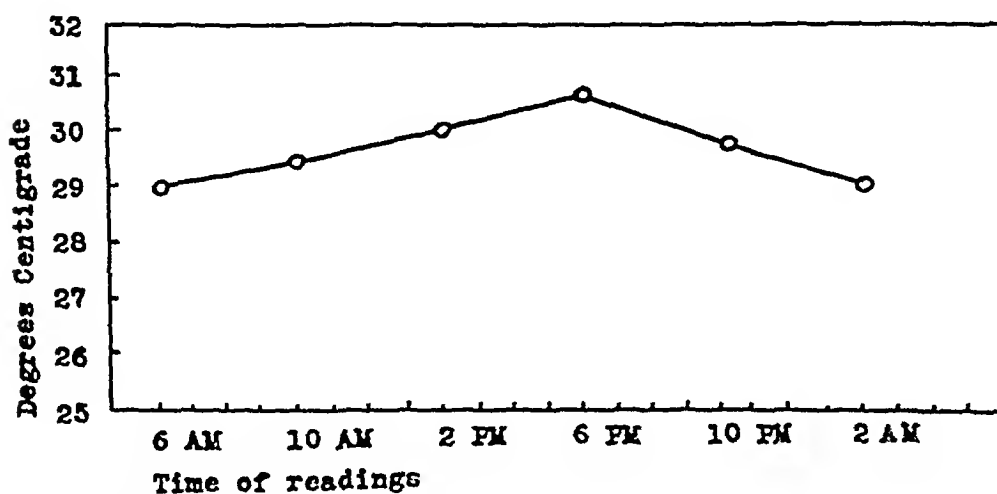


CHART 2 Surface temperature readings in case I showing a higher level after the gangrene had been healed by the use of acetylcholine

day for one month resulted in healing of the gangrene and the return of arterial pulsations in the feet

Treatment was discontinued for the following two months, at the end of which time examination disclosed no signs of the previous vascular disturbance

Case III A man, 84 years of age, had complained of pain in the right leg on exercise for three years. Lately this had become steadily worse. Two weeks before the present observation he was seized with severe pain in the member which lasted twenty-four hours. This was evidently due to an acute arterial occlusion since he noticed bluish discoloration of the toes for the first time. Following this attack he suffered with constant pain in the leg which interfered with sleep.

Palpation showed absence of pulsations in the popliteal, dorsalis pedis and anterior tibial vessels of both sides while rubor with dependency and blanching with elevation of the right foot was marked. The skin over the weight bearing areas of the right foot was thickened and there was a small ulcer both on the lateral surface and on the heel.

The surface temperature of the right foot was 25° and of the left 26° C. One hour after the intramuscular administration of 100 mg of acetyl-choline the surface temperatures were 28° . There was a gradual drop to the previous level at the end of

twenty-four hours (chart 4). Marked amelioration of rest pain was obtained by the use of the drug given every other day for the next two weeks. Its continuation twice weekly during the following two months produced marked improvement in the trophic changes and complete cessation of pain. The peripheral vessels remained pulseless.

SUMMARY

Three patients having trophic lesions due to vascular disease of the extremities were treated by intramuscular injections of acetyl-choline hydrochloride. Healing of gangrenous areas, relief of pain and elevation of the surface temperature to a higher level was obtained by the use of the drug. In one case pulsations in the peripheral arteries were re-established.

In one to three hours following an injection the cutaneous temperature in the affected parts was increased 2° to 5° C. This elevation lasted eighteen to twenty-four hours and was accompanied by a sense of warmth and relief of pain in the extremities.

The advantages of the use of acetyl-choline are (1) the ease of its admin-

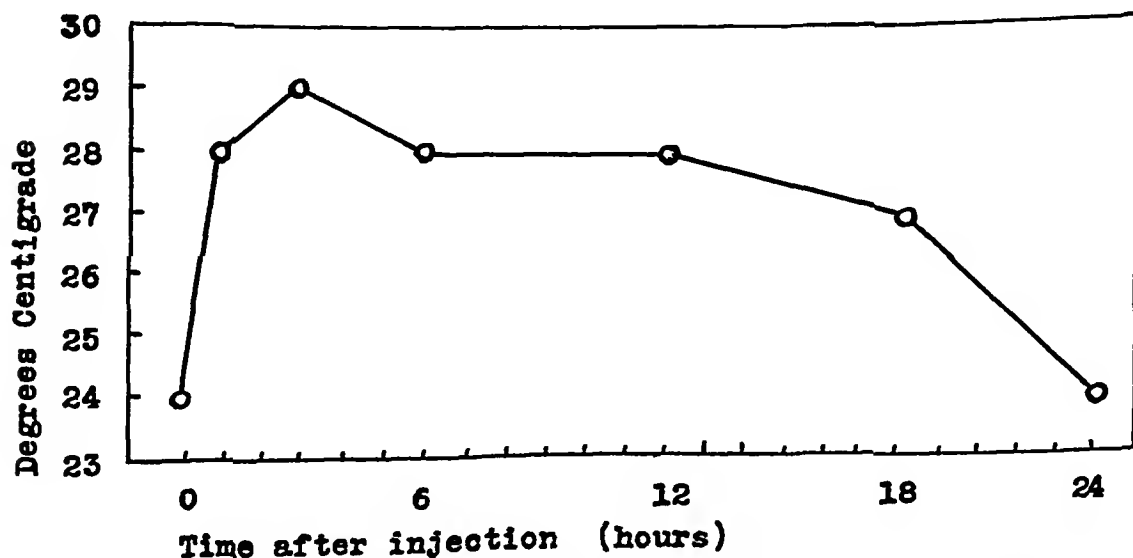


CHART 3 Surface temperature readings in case II after the injection of 100 mg of acetyl-choline

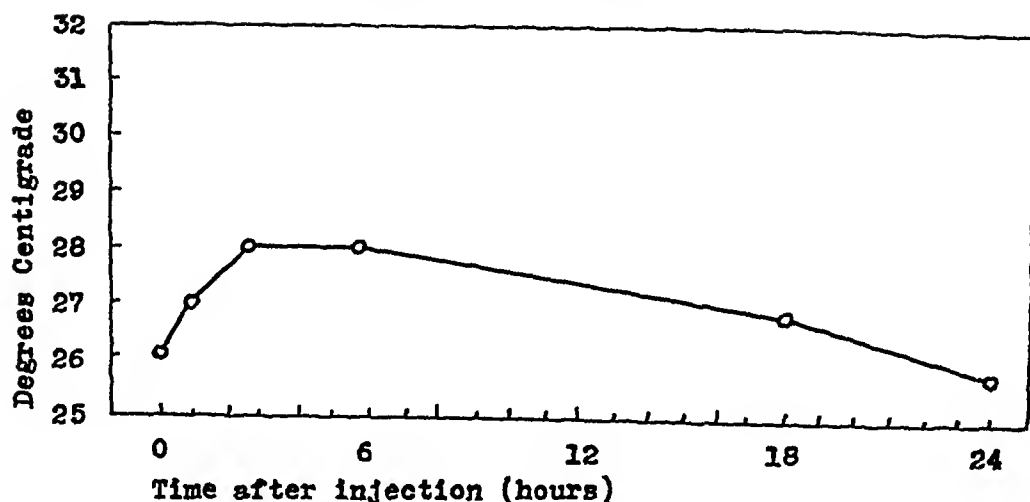


CHART 4 Surface temperature readings in case III after the injection of 100 mg of acetyl-choline

istration, (2) the absence of constitutional reactions following its use, and (3) the ability to maintain a constant and uniform elevation of the surface temperature by frequently repeated injections

REFERENCES

- ¹SAMUELS, S S Treatment of gangrene due to thrombo-angitis obliterans, Jr Am Med Assoc, 1931, xcvi, 751-754
- ²BUERGER, L Circulatory diseases of the extremities, 1924, W B Saunders Co, Philadelphia
- ³MEYER, W Etiology of thrombo-angitis obliterans, (Berger), Jr Am Med Assoc, 1918, lxxi, 1268-1272
- ⁴STEFEL, W A Sodium citrate treatment of thrombo-angitis obliterans Jr Am Med Assoc, 1921, lxxvi, 429-431
- ⁵STERN, W G Blood viscosity in trophic disturbances of circulation Jr Bone and Joint Surg, 1924, xvii, 902-908
- ⁶BROWN, G E Treatment of peripheral vascular disturbances of the extremities, Jr Am Med Assoc, 1926, lxxxiii, 379-383
- ⁷ALLEN, A W, and SMITHWICK, R H Use of foreign protein in the treatment of peripheral vascular diseases, Jr Am Med Assoc, 1928, cxvi, 1161-1168
- ⁸SPURLING, R G Status of surgery of the sympathetic nervous system, South Med Jr, 1930, xxi, 294-298
- ⁹VILLARET, M, and JUSTIN-BESANCON, L Syndrome de Raynaud, etude des pressions venéuse et capillaire, action de l'histamine et de l'acetylcholine, Bull et mém Soc med de hop d Paris, 1926 I, 465-472
- ¹⁰VILLARET, M, and JUSTIN-BESANCON, L The practical application of acetylcholine Med Jr and Rec, 1929, cxliii, 343-345
- ¹¹VILLARET M, SCHIFF-WERTHEIMER, and JUSTIN-BESANCON L Effets de l'injection sous-cutanée d'acetyl-choline sur l'artère radiale de l'homme, Compt rend Soc de biol, 1928 cxviii, 909-911
- ¹²VILLARET, M, and JUSTIN-BESANCON, L The therapeutic use of acetyl-choline Med Jr and Rec, 1930, cxliii, 35-38
- ¹³ANDERSON, A W and BROWN, G E Thoracic and lumbar sympathetic ganglionectomy in peripheral vascular diseases therapeutic value Jr Am Med Assoc 1930 cxvi, 250-252

Metastatic Malignant Tumors of the Brain*†

By HAROLD F DUNLAP, M.D., *Rochester, Minnesota*

IN THE diagnosis and treatment of tumors of the brain, one is always confronted by the possibility of any given tumor being secondary to some primary malignant tumor situated outside of the central nervous system. Many difficulties, however, are encountered in attempting to prove the metastatic origin of such a tumor. In the hope of gaining some knowledge which would aid in clinical recognition of the true nature of these lesions, a clinical, statistical, and pathologic survey of the material available at The Mayo Clinic was undertaken.

Ninety-five patients examined in The Mayo Clinic in the ten years ending January 1, 1929, were given a diagnosis of metastatic malignant tumor of the brain. This series of cases, for purposes of study, has been divided into three groups. Group 1 consisted of twenty-three cases in which complete necropsy, including examination of the brain, was performed. In each of these cases diagnosis was first made from gross appearance of the tumor; a primary malignant tumor outside of the central nervous system was found in each case, and at least one secondary malignant tumor was found within the brain. These diagnoses all were con-

firmed by microscopic examination. Group 2 consisted of forty-four cases in which there was a clinical picture of tumor of the brain but in which there was no gross or microscopic examination, of any kind, of brain tissue. However, the presence of a primary malignant tumor outside of the central nervous system was confirmed in each case by necropsy, by biopsy, or by operation at a time previous to the appearance of symptoms of tumor of the brain. This confirmatory examination included, in all cases, microscopic studies. Group 3 consisted of twenty-eight cases in which there was a clinical picture of tumor of the brain and also a clinical picture of primary malignant tumor outside of the central nervous system. In this group gross or microscopic examination of tissue was not made at the clinic. However, some of the patients previously had been operated on elsewhere, at which time a diagnosis of malignant tumor outside of the central nervous system had been made. These diagnoses in some instances had been substantiated by microscopic studies. Detailed neurologic studies were conducted in eleven cases of group 1 and in seventy-seven cases of the entire series.

In none of the ninety-five cases was there metastasis to the skull without evidence of intracranial involvement.

*Received for publication July 30, 1931.

†From the Division of Medicine, The Mayo Clinic.

and in none was the intracranial involvement by direct extension, such as occurs in cases of tumor of the nasopharynx, accessory nasal sinuses, orbits, or eyes

The diagnoses of the primary and secondary tumors of group 1 were made by the Section on Pathologic Anatomy of The Mayo Clinic. Emphasis in this study was placed on the reaction of the tissue of the brain to the presence of the tumor, rather than on study of the nature of the tumor. The first eleven cases of group 1 were selected for special pathologic study. Sections for microscopic examination were taken from several regions from the juncture of the tumor and the adjacent tissue of the brain, from the surface of the cortex at points distant from the tumor, and from the choroid plexus. Stains used in each instance were hematoxylin and eosin, iron hematoxylin, Scharlach R, toluidine blue, van Gieson's and Mann's

ANALYSIS OF MATERIAL

The cases comprising groups 2 and 3, in which the malignancy of the cerebral lesion had not been authentically determined, although the clinical picture was that of a primary malignant tumor outside of the central nervous system and a secondary tumor within the brain, have been subjected to clinical and statistical analysis. The results of the survey of the cases of group 1 are compared to a similar survey of the larger series of cases comprising groups 2 and 3.

Clinical Studies The average age of the patients of the entire series of ninety-five cases was 47.5 years. There were only twelve patients who were less than thirty-five years of age, of

whom three were children who probably were suffering from primary tumors of the suprarenal gland. Thus, the average age of the patients falls within the accepted cancer age. In spite of the high incidence of metastasis to the brain from carcinoma of the breast, which would tend to increase the number of cases among women, cases were about evenly divided between the sexes. There were forty-nine males and forty-six females. There was an average loss of weight of 24 pounds in thirty-four cases in which the weight of the patients had been accurately recorded.

An attempt was made in those cases in which the primary lesion should have been readily recognized, as in cases of carcinoma of the breast and in those cases in which the onset of symptoms referable to the primary lesion could be fairly accurately determined, to estimate the duration of existence of the primary lesion prior to the onset of cerebral symptoms. The average thus obtained was twenty-one months for the cases of group 1, and 31.5 months for the cases of each of the other groups. The longest interval between the onset of symptoms of the primary lesion and of those of the cerebral lesion in a case of group 1 was 6.5 years, the primary tumor was a hypernephroma. The corresponding interval in a case of group 2 was nine years, the primary tumor was a carcinoma of the carotid body. The interval in a case of group 3 was twelve years, the primary tumor was a carcinoma of the breast.

The onset of cerebral symptoms had antedated the patient's visit to the clinic for an average of three months.

for the cases of group 1, and for 45 months for the cases of each of the other groups

The average length of life from the time of examination at the clinic, until death, was 35 months, and the time from onset of cerebral symptoms until death was eight months in those cases of groups 2 and 3 in which the time of death had been reported

The presenting symptoms in the entire group of ninety-five cases were directly referable to the cerebral lesion in sixty-eight and to the primary lesion in only fifteen. There were symptoms referable to both the primary and the cerebral lesion in twelve of the cases. In seven cases of group 1 in which the patients presented themselves at the clinic because of cerebral symptoms, mention was not made of symptoms referable to the primary lesion. Cerebral symptoms were merely a terminal feature in twelve cases of group 1.

The symptoms referable to the cerebral lesion most frequently complained of were headache, vomiting that often was of a projectile nature, disturbances of vision and of speech, vertigo, and transient aphasia. Headache was the predominant complaint. The clinical signs most frequently noted were monoplegic or hemiplegic paresis, cranial nerve palsy, ataxia, and Jacksonian seizures.

The frequent incidence of mental disturbance is very striking in all three groups. In study of mental disturbance, only those cases were used which had been observed by the Section on Neurology of The Mayo Clinic. Definite mental changes were observed in 75 per cent of the cases of group 1, in 45 per cent of the cases of group 2,

and in 56.5 per cent of the cases of group 3, the incidence for the entire series was 57 per cent. The mental disturbance varied from mental sluggishness, to confusion and even to stupor in the more advanced cases. Emotional disturbances of varying degree and duration were present in a smaller percentage of cases.

Of the eighty-four cases of the entire ninety-five in which the ocular fundi had been examined, choked disk was recorded in 40 per cent. Likewise, in 41 per cent of those cases of group 1 in which the fundi had been examined there was choked disk. Optic atrophy and hemianopsia were present in a smaller percentage of cases of the entire group. There were nine cases in which there were perimetric visual field defects and three cases in which optic atrophy was present.

Study of the clinical localization of the cerebral tumors failed to disclose any region of predilection for the development of metastasis in the brain (table 1). The sixteen cases of group 1, in which detailed neurologic studies had been conducted, and in which necropsy, including examination of the

TABLE 1
Clinical Situation of Tumor of the Brain of the Seventy-seven* Patients Who Underwent Neurologic Examination

Situation	Groups			Total
	1	2	3	
Right side of cerebrum	2	11	6	19
Left side of cerebrum	2	9	4	15
Chiasma			1	1
Cranial nerves		3	3	6
Brain stem	1	3	2	6
Cerebellum	1	5		6
Base		2		2
Gasserian ganglion		1		1
Third ventricle		2		2
Meninges	1			1
Not stated	9	9	6	24

*Diagnosis was of involvement of more than one region in some cases.

brain, had been performed, were the only cases in which clinical diagnosis and localization could be checked accurately against pathologic changes. The situation of the cerebral lesion was correctly diagnosed in seven of the sixteen cases. In the remaining cases of the sixteen either localizing signs were absent or dissemination of the signs led to incorrect diagnosis of an inflammatory lesion.

A clinical diagnosis of metastatic malignant tumor of the brain was made in six of the sixteen cases. In these six cases there was an obvious primary malignant tumor elsewhere than in the brain, recognizable metastasis, or a history of previous operation for a malignant tumor situated outside of the central nervous system.

A diagnosis of primary tumor of the brain had been made in five of the sixteen cases, none of which presented either symptoms or signs referable to a primary lesion elsewhere. However, the primary lesion proved to be carcinoma of the lung in three cases and carcinoma of the kidney in two cases.

In the preceding two paragraphs, eleven of a particular group of sixteen cases have been considered. In the remaining five of these sixteen cases the dissemination of signs, the paucity of localizing signs, and failure to recognize or sufficiently to consider the primary lesions led to the assumption that the cerebral manifestations were on the basis of inflammatory diseases. In one of these five cases in which a clinical diagnosis of tuberculosis of the lung, spine and brain had been made, necropsy disclosed a primary carcinoma of the lung with metastasis to four vertebrae, situated partly in the thoracic and partly in the

lumbar region, to the subjacent meninges in the thoracic region, and to the brain. In the second of the five cases, in which a diagnosis of syphilis of the central nervous system had been made, necropsy disclosed a primary carcinoma of the lung, with metastasis to the meninges covering the midbrain and cerebellum, and healed pulmonary tuberculosis. In the third of the five cases, in which the clinical diagnosis was infectious meningo-encephalitis, secondary to the toxemia of pregnancy of seven months, necropsy revealed multiple, bilateral metastatic nodules in the cerebrum and cerebellum, secondary to carcinoma of the breast, for which operation had been performed three years previously. In the fourth of the five cases, in which a clinical diagnosis of recurrent carcinoma of the sigmoid had been made, and in which at necropsy a metastatic nodule had been found in the cerebellum a clinical diagnosis of general paralysis of the insane had been made in view of an old history of syphilis, rapidly developing and marked mental deterioration, and the presence of clinical signs considered characteristic of syphilis of the nervous system. The fifth patient of these five, who was brought to the hospital in a moribund state, was found at necropsy to have a primary carcinoma of the pancreas, with generalized carcinomatosis and multiple cerebral metastatic growths.

There were five cases in group 1 in which there was carcinomatous involvement of the meninges. Two cases in which the primary lesion was an asymptomatic carcinoma of the lung have been considered in the preceding paragraph. In a third case, one of car-

cinoma of the stomach presenting terminal cerebral manifestations, a clinical diagnosis of carcinomatous meningitis secondary to gastric carcinoma was made prior to death, and this diagnosis was substantiated at necropsy by demonstrating carcinomatous invasion of the pia-arachnoid. In a fourth case, one of carcinoma of the breast in which cerebral symptoms were terminal, but in which neurologic studies had not been conducted, necropsy disclosed carcinomatous invasion of both the dura and pia-arachnoid. A clinical diagnosis of inoperable carcinoma of the breast, with metastasis to the midbrain, was made in a fifth case, in which necropsy disclosed several regions of metastasis to the cerebral cortex; there was also metastasis to the substance of the left third cranial nerve and to the pia-arachnoid covering the midbrain with extension of the tumor cells along the pial prolongations into the subjacent brain.

Laboratory Studies There was a slight to a moderate degree of anemia in 28 per cent of eighty-eight cases in which blood counts had been made. Of eighty cases in which Wassermann tests of the blood had been made, a positive reaction occurred in only one instance.

Examination of spinal fluid had been conducted in twenty-two cases. Among these twenty-two there was one instance in which the Wassermann test of the spinal fluid was positive, but in this instance the Wassermann test of the blood was negative. Yellow spinal fluid was obtained in six cases, three of which belong in group 1, and in which, at necropsy, involvement of the ventricle or meninges by metastatic lesion was found. There were not

more than eleven cells for each cubic millimeter of spinal fluid in any case.

Roentgenologic methods failed to reveal the presence of many of the growths encountered. The entire experience was as follows. Roentgenograms of the thorax had been made in seventy-eight cases, in 47.5 per cent of which there was evidence of pathologic change. A diagnosis of primary or metastatic malignant growth of the lung was correctly made in 37 per cent of the cases. Of the fourteen cases of group 1 in which roentgenograms of the thorax had been made and in which at necropsy pulmonary metastasis had been demonstrated, evidence of pathologic change in the roentgenogram was reported in eight cases (57 per cent). However, the incorrect diagnosis of inflammatory lesion had been made in four of the eight cases.

Metastasis or other pathologic changes had been reported in 21 per cent of the sixty-three cases in which roentgenograms of the head had been made.

Pathologic Studies The lung, breast and kidney were the sites of the primary lesion in fifty-one of the ninety-five cases, an incidence of 53.6 per cent of those cases in which the site of the primary growth could be determined. Thirteen of these fifty-one cases were in group 1, that is, 25.6 per cent of the cases comprising group 1 (table 2).

It will be recalled that the nature of the primary lesion, outside of the central nervous system, was determined by microscopic studies in all cases of groups 1 and 2. The cases in which the diagnosis was carcinoma, hypernephroma or melano-epithelioma were classed together as cases of carcinoma,

TABLE 2
Situation of the Primary Malignant Tumors
in all Cases Studied

Situation	Groups			Total
	1	2	3	
Breast	5	20	3	12
Kidney	3	4	5	12
Lung	5	1	3	9
Skin	2	3		5
Suprarenal gland	2		3	5
Colon	2	1	1	4
Thyroid gland	1	1	2	4
Stomach	1	1	1	3
Testis		2	1	3
Bone		2	1	3
Esophagus			1	1
Pancreas	1			1
Gallbladder		1		1
Prostate gland			1	1
Uterus		1		1
Tonsil		1		1
Parotid gland		1		1
Carotid body		1		1
Eye		1		1
Undetermined	1	3	4	8

whereas the cases in which the diagnosis was sarcoma, lymphosarcoma, and Hodgkin's disease were classed together as cases of sarcoma. In fifty-nine cases the growths were classified as carcinomas, an incidence of 88 per cent of the cases comprising groups 1 and 2. Six cases in which the growths were classified as sarcomas and one case each in which they were classified as myeloma and as neuroblastoma accounted for the remaining 12 per cent of the cases.

In general, metastasis was widespread throughout the body. Pulmonary involvement, either primary or secondary, was proved in nineteen of the twenty-three cases which composed group 1, an incidence of 82.6 per cent of the cases. There were five cases of primary carcinoma of the lung and fourteen cases of metastasis to the lung. This leaves four cases of group 1 to be accounted for. Two of these in which metastasis to the lung did not occur, were cases of carcinomatous meningitis in which the brain tissue

proper was not invaded. Of the two remaining cases, one was a case of sarcoma which had metastasized throughout the body in the fat-bearing tissues, and the other was a case of melanopitheliomatosis.

In the cases of group 1, in which metastasis occurred to the tissue of the brain, secondary nodules were found to be scattered irregularly throughout the gray and the white matter, just as in clinical examination, so in this examination, no site of predilection for the development of metastasis was noted. The tumors were usually rather sharply demarcated from the adjacent brain tissue and often were the site of rather marked necrosis and hemorrhage. Metastasis was single in seven cases and multiple in thirteen. It seems appropriate here to call attention to the case in which more than thirty metastatic nodules were counted. In the remaining three cases the involvement was confined primarily to the pia-arachnoid (figure 1).

Microscopic examination in most instances confirmed the impression that masses were rather sharply demarcated from the adjacent tissue, but in only two cases was a definite fibrous capsule present (figures 2 and 3). The tumors were usually decidedly vascular, and there was hemorrhage into the tumor. The tumors in some instances were composed of solid masses of tumor cells undergoing various stages of degeneration, whereas in other instances the tumor cells occurred singly, or as islets of tumor cells in a well-preserved state. The amount of reaction in the tissue of the brain adjacent to the tumor appeared to vary with the size and type of the tumor, it was less in the small tumors and in the two



FIG. 1 Case 10 Small pearly white metastatic nodules scattered over inner surface of dura



FIG. 2 Case 1 The zone of demarcation, with a fibrous capsule, dividing the brain below from the tumor focus above. Rarefied appearance and swollen astrocytes in the subjacent brain tissue ($\times 75$)



FIG. 3 Case 3 Demarcation zone dividing the brain tissue from the tumor focus, without a capsule of connective tissue. Rarefaction and mild glial proliferation ($\times 75$)

cases of melano-epithelioma, as compared to the cases of carcinoma. This zone frequently presented a rarefied or sieve-like appearance (figures 4 and 5). The number and size of the blood vessels were usually increased, and frequently they formed the center of an outlying focus of tumor cells. Frequently tumor cells and scavenger cells could be demonstrated adjacent to and in the perivascular spaces of blood vessels in this zone. There was astrocytic proliferation, and in case of involvement of the gray matter, marked destruction of the ganglion cells. In the brain tissue distant from the tumor there were usually only slight changes. This zone occasionally appeared rarefied. There was usually proliferation of the astrocytes, and occasional gitter cells. Satellitosis was commonly observed in the cortex. In two cases the choroid plexus was invaded by tumor cells. There was no invasion of the meninges secondary to invasion of the tissue of the brain, except when the tumor came into direct contact with the surface of the brain. There was an occasional inflammatory reaction in the meninges, as evidenced by increased vascularity and the presence of lymphocytes, polymorphonuclear leukocytes, plasma cells, and erythrocytes, especially if the tumor was in close proximity to the surface of the brain.

In cases of carcinomatous meningitis the subarachnoid space was distended with tumor cells existing singly or as masses (figure 6). There was a moderate amount of proliferation of connective tissue. Lymphocytes, polymorphonuclear leukocytes, plasma cells and erythrocytes were found interspersed between the tumor cells. In

some sections the tumor cells were found extending along pial prolongations into the sulci and invading the subjacent cortex (figures 7 and 8). There was little reaction in the tissue of the brain except for mild, generalized glial proliferation.

COMMENT AND COMPARISON OF THIS SERIES WITH OBSERVATIONS AND OPINIONS IN THE LITERATURE

The literature dealing with secondary carcinoma and sarcoma of the brain has been ably reviewed by Kaufmann, Gallavardin and Varay, Maass, Liebenfeld and Benda, Hennemann, Beerman, Humbert and Alexieff, Walshe, Lissauer, Schwarz and Bertels, Meyer and Grant.

Krasting gave the ratio of 1:3 as the incidence of metastatic to primary tumors of the brain at the Basel Hospital for a period of thirty-five years. This figure, obtained from the post-mortem service of a large general hospital, does not hold for the clinical incidence in a large diagnostic center. Sixty-one cases of metastatic tumor of the brain and 1,308 cases of primary tumor of the brain were seen at The Mayo Clinic from 1919 to 1925 inclusive, giving a ratio of 1:20 for secondary to primary tumors of the brain. This figure is in close agreement with that of Grant, who reported an incidence of 4 per cent for secondary as compared to primary tumor of the brain from the Peter Bent Brigham Hospital.

Krasting, in a review of 12,730 postmortem examinations performed at the Basel Hospital from 1870 to 1905, reported 1,078 cases of carcinoma, in 817 of which the brain had been examined and 160 cases of sarcoma,



FIG 4 Case 11 Islets of tumor cells extending into the adjacent brain with intervening brain tissue forming the so-called transition zone ($\times 75$)

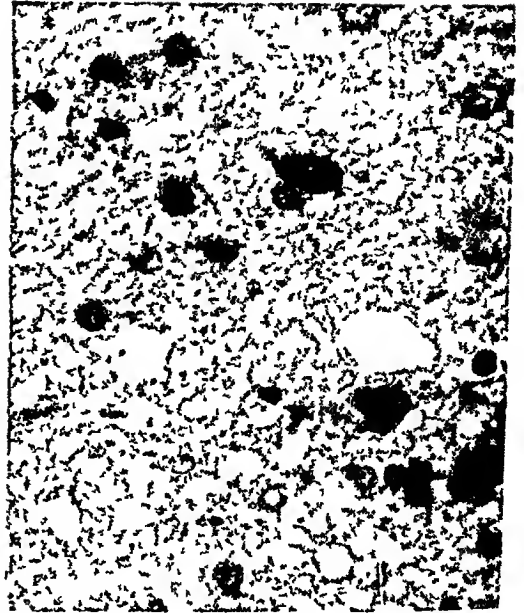


FIG 5 Case 1 Brain tissue adjacent to the tumor Rarefaction and formation of gemastite glial cells ($\times 350$)

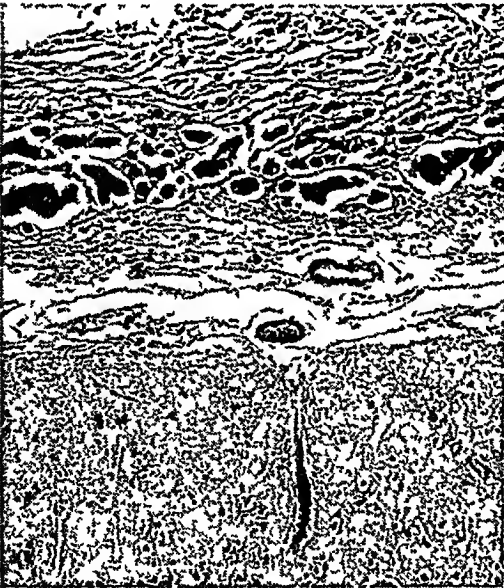


FIG 6 Case 10 Carcinomatous meningitis, tumor cells occur either singly or as masses The subjacent cortex is represented, and there is a blood vessel running in from the surface Neither the perivascular space, nor the tissue of the brain proper is involved by the tumor cells ($\times 75$)



FIG 7 Case 6 Extensive involvement of the pia-arachnoid in a case of carcinomatous meningitis with extension of the tumor cells along the pial prolongations and involvement of the adjacent cerebellar tissue ($\times 75$)

in 118 of which the brain had been examined. The incidence of metastasis, in those cases in which the brain was examined, was 57 per cent for the group with carcinoma and 11.6 per cent for the group with sarcoma. Gallavardin and Varay placed the incidence of metastasis to the brain as once in every seventeen to eighteen cases of malignant tumor.

Metastasis in general is widespread throughout the body in those cases in which there is cerebral metastasis. The lung was involved, either primarily or secondarily in 83 per cent of those cases in this series in which necropsy was performed. This tends to substantiate Kaufmann's view that pulmonary metastasis enhances cerebral metastasis.

Metastatic growths in the brain, in those cases in which authors have given their number, usually have been multiple and diffusely scattered. Metastatic growths in the tissue of the brain were multiple in 65 per cent of my series and in 66 per cent of Globus and Selinsky's series.

The incidence of localization of the metastatic growths in various parts of the brain appears to vary with the authors' individual experience. My series discloses no especial site of localization for the metastatic growths. Gallavardin and Varay found the largest proportion of metastatic growths in the cerebrum. Ewing, in writing of carcinoma of the breast, stated that they may metastasize to any part of the brain but are especially likely to metastasize to the cerebellum. Spiller and Weisenberg found involvement of the central convolutions, the cerebellum and the temporal lobes in order of frequency in which they are named.

It is generally agreed that the tissue of the brain is more often involved than the meninges. Cranial nerves are occasionally involved, either directly through metastasis to the substance of the nerve, or indirectly at their point of emergence from the meninges, when the latter are invaded by the tumor cells.

There is considerable variation of opinion as to the amount of reaction which the presence of the tumor excites in the surrounding tissue of the brain. Fried expressed the belief that there is no reaction, that the tissue of the brain merely melts away before the advance of the tumor. Buchholz, Kolpin, and Gallavardin and Varay stated that the tissue of the brain is merely pushed aside by the advance of the tumor, without actually being destroyed and without provoking reactive phenomena. Heinenmann, Conighi, Morse and Fischer have reported on this aspect of the subject. Hassin and Singer re-

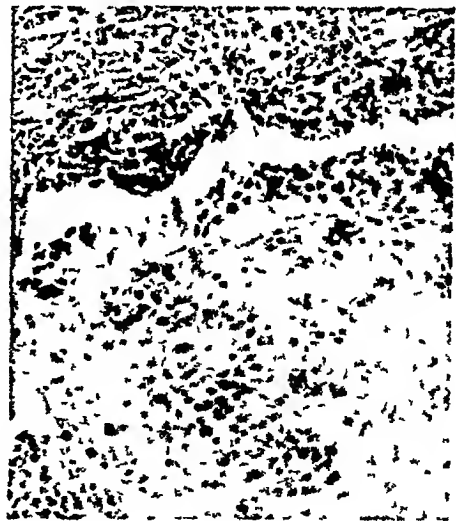


FIG. 8. Case 5. Extensive neoplastic invasion of the pons and medulla over the brain with small foci of tumor cells penetrating the subjacent cortex (x 75).



FIG 4 Case 11 Islets of tumor cells extending into the adjacent brain with intervening brain tissue forming the so-called transition zone ($\times 75$)

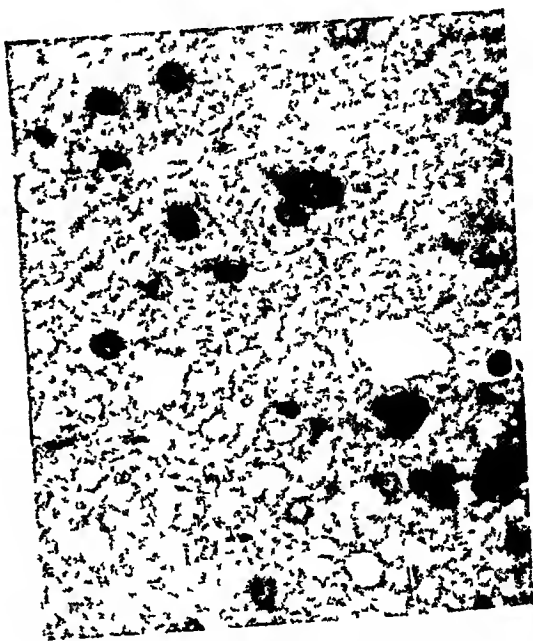


FIG 5 Case 1 Brain tissue adjacent to the tumor Rarefaction and formation of gemastite glial cells ($\times 350$)

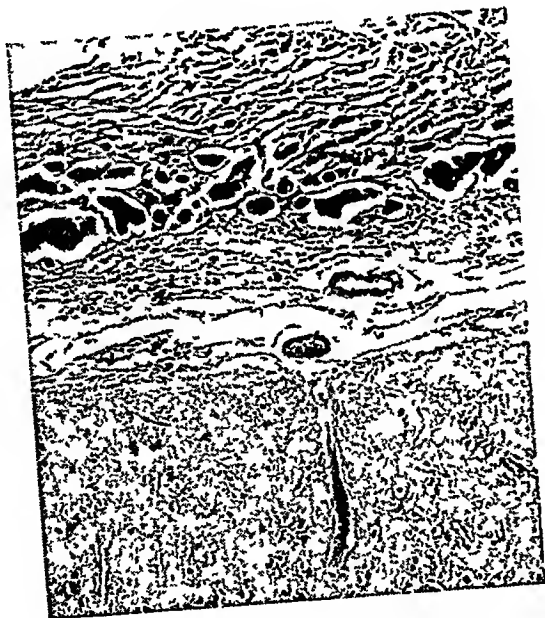


FIG 6 Case 10 Carcinomatous meningitis, tumor cells occur either singly or as masses The subjacent cortex is represented, and there is a blood vessel running in from the surface Neither the perivascular space, nor the tissue of the brain proper is involved by the tumor cells ($\times 75$)



FIG 7 Case 6 Extensive involvement of the pia-arachnoid in a case of carcinomatous meningitis with extension of the tumor cells along the pial prolongations and involvement of the adjacent cerebellar tissue ($\times 75$)

in 118 of which the brain had been examined. The incidence of metastasis, in those cases in which the brain was examined, was 57 per cent for the group with carcinoma and 11.6 per cent for the group with sarcoma. Gallavardin and Varay placed the incidence of metastasis to the brain as once in every seventeen to eighteen cases of malignant tumor.

Metastasis in general is widespread throughout the body in those cases in which there is cerebral metastasis. The lung was involved, either primarily or secondarily in 83 per cent of those cases in this series in which necropsy was performed. This tends to substantiate Kaufmann's view that pulmonary metastasis enhances cerebral metastasis.

Metastatic growths in the brain, in those cases in which authors have given their number, usually have been multiple and diffusely scattered. Metastatic growths in the tissue of the brain were multiple in 65 per cent of my series and in 66 per cent of Globus and Sehnsky's series.

The incidence of localization of the metastatic growths in various parts of the brain appears to vary with the authors' individual experience. My series discloses no especial site of localization for the metastatic growths. Gallavardin and Varay found the largest proportion of metastatic growths in the cerebrum. Ewing, in writing of carcinoma of the breast, stated that they may metastasize to any part of the brain but are especially likely to metastasize to the cerebellum. Spiller and Weisenberg found involvement of the central convolutions, the cerebellum and the temporal lobes in order of frequency in which they are named.

It is generally agreed that the tissue of the brain is more often involved than the meninges. Cranial nerves are occasionally involved, either directly through metastasis to the substance of the nerve, or indirectly at their point of emergence from the meninges, when the latter are invaded by the tumor cells.

There is considerable variation of opinion as to the amount of reaction which the presence of the tumor excites in the surrounding tissue of the brain. Fried expressed the belief that there is no reaction, that the tissue of the brain merely melts away before the advance of the tumor. Buchholz, Kolpin, and Gallavardin and Varay stated that the tissue of the brain is merely pushed aside by the advance of the tumor, without actually being destroyed and without provoking reactive phenomena. Heinemann, Conighi, Morse and Fischer have reported on this aspect of the subject. Hassin and Singer re-

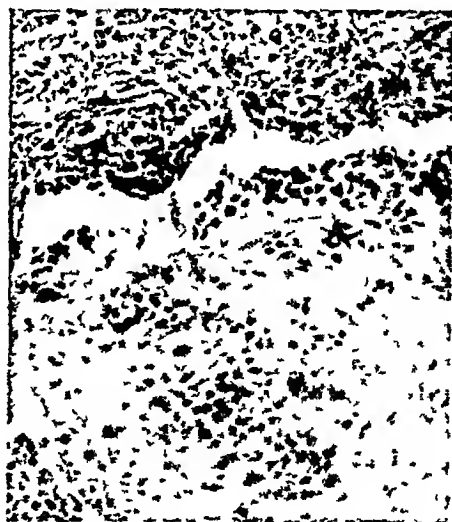


FIG. 8. Case 5. Extensive ependymal invasion of the pialarachnoid over the surface of the brain with small foci of tumor cells penetrating the underlying cortex ($\times 75$).

ported focal (masses) and diffuse (encephalitic) lesions in cases of secondary carcinoma involving the tissue of the brain. They expressed the belief that there are generalized reactive phenomena characterized by the formation of new capillaries and proliferation of glial cells, and that there are degenerative changes in the ganglion cells most marked in the tissue of the brain adjacent to the tumor. In the pia-arachnoid and the choroid plexus dilated vessels were constantly present, and there were lymphocytes and gitter cells. In carcinoma of the meninges, the only pathologic element found outside the tumor cells was the presence of gitter cells, plasma cells, and macrophages in the pia-archnoid, and some proliferation of glial cells in the subjacent cortical tissue.

In the eleven cases of group 1 (paragraph 5) in this series in which detailed microscopic studies were made of sections taken from the tumor, of the adjacent tissue of the brain and of tissue of the brain distant from the tumor, the pathologic changes were essentially in agreement with those of Hassin and Singer.

The incidence of metastasis to the brain varies considerably with the situation and nature of the primary tumor. The general consensus of opinion appears to be that a primary carcinoma which gives rise to secondary tumor of the brain is most likely to be in the lung or breast, and that a primary sarcoma which gives rise to secondary growth in the brain is most likely to be in the skin or lymph nodes. Ewing and Krasting expressed the belief that melanotic tumors of the skin are especially prone to metastasize to the brain.

Maass, in a study of carcinomatous meningitis, found the stomach, lungs, and breast to be the site of the primary tumor in the order in which they are named. Fried, in a study of nineteen cases of primary carcinoma of the lung in which necropsy was performed, found cerebral metastasis in nine of eleven cases in which the brain was removed. He expressed the belief that the greater incidence of metastasis to the brain from primary malignant tumor of the lung, as compared to malignant tumors of other organs, is due to the fact that the lung acts as a filter in case of metastasis from other organs, whereas there is no natural barrier between the brain and the lung. Krasting, in a review of 130 cases of cerebral metastasis, found the primary lesion in the breast in forty cases, and in the lung in twenty-nine cases, an incidence for these two organs of 50 per cent of the entire series. I find, by including the kidney along with the lung and breast, that metastasis to the brain arose from one of these three organs in 56 per cent of Krasting's series, in 51 per cent of Grant's series, in 56.5 per cent of my series, and in 54 per cent of ninety-four cases in which the situation of the primary tumor was stated, among 108 cases which I reviewed indiscriminately from the literature.

Little difficulty should be encountered in recognizing the primary tumor when it is in the breast. Tumors in the lung and kidney, however, are prone to run an asymptomatic course. At other times, the cerebral manifestations so overshadow any symptoms which may be referable to the primary lesion that the true nature of the malady is not recognized. Fried stated

that in cases of primary carcinoma of the lung there may be symptoms referable to the thorax, the condition may run a silent course, or there may be symptoms referable to the metastases only. He expressed the belief that the clinical features are amazingly scant as compared to the amount of tissue involved and the grave nature of the lesion. His opinion was that metastasis to the brain occurs early, often masking the clinical picture of the primary lesion. In his series of cases of primary carcinoma of the lung, five patients presented symptoms due to the cerebral metastasis, the primary pulmonary lesion was discovered only accidentally following operation on the brain or at necropsy. Seven of the eight cases in my series of proved primary carcinoma of the kidney or lung with metastasis to the brain, were accompanied neither by symptoms, nor, with one exception, by clinical signs referable to the primary lesion.

Silent primary tumors, and foci of metastasis may exist in other organs, as illustrated in a case of group 3 in which a primary carcinoma of the prostate gland had metastasized to the lungs, spine and brain without symptoms referable to any lesion except the cerebral one. Cerebral symptoms had been noted for an average period of three to four months prior to the time of examination. Grant reported an average interval of four months between the onset of cerebral symptoms and the time of examination.

Choked disks occurred in 40 per cent of the cases. This is practically the same incidence of occurrence as in primary tumor of the brain. Likewise the degree of choking varies as much as in primary tumors of the brain. In

my study the cerebral symptoms and signs were frequently of a bizarre and disseminate nature, varying in intensity from day to day. In cases of multiple metastasis, a single lesion situated in a vital center may give origin to the cerebral symptoms and signs noted, the other lesions may be in silent regions. Globus and Selmsky stated that multiplicity of lesions will, in the majority of cases, lead to dissemination of objective signs.

Mental disturbance appears to be one of the outstanding features in metastatic tumors of the brain. The mental symptoms associated with metastatic tumor of the brain appear to be more marked than those associated with primary tumor of the brain. The presence and severity of mental symptoms appeared to bear possible relationship to the presence and severity of the encephalitic changes in all cases except one. Lewis reported a case in which there had been a sudden onset of psychic manifestations diagnosed by several eminent psychiatrists as a catatonic type of dementia precox, on the later development of neurologic signs, the diagnosis had been changed to encephalitis, and it was not until necropsy that it was learned that the symptoms were due to cerebral metastasis from a primary malignant growth probably in the lung. Mental symptoms occurring with metastatic tumor of the brain may be readily confused with those occurring in the ordinary type of psychosis. The similarity of such symptoms to those of general paralysis of the insane has been reported by Smith, Siefert, Lilholtz and von Heyde and Curschmann. Van Hasselt reported a case in which the diagnosis was acute dementia

Maass reported a case presenting acute psychosis with Korsakoff's syndrome. Heinemann stated that the clinical picture may be that of alcoholic intoxication. Morse expressed the belief that a psychic disturbance with stupor is often the outstanding feature. Elzholtz stated that a confusional state is the usual type of mental disturbance.

It is usually rather difficult to establish clinically that a tumor of the brain is metastatic, for the symptoms referable to the cerebral lesion are often essentially the same as those presented by a primary tumor of the brain. Moreover, the primary lesion may be a silent one, or the cerebral symptoms may be so pronounced as to obscure the less obvious symptoms and signs referable to the primary tumor. At other times, especially if there is carcinomatous involvement of the meninges, the clinical picture mimics some inflammatory lesion or functional disturbance. At times, obtaining accurate data as to symptoms, signs, and laboratory studies essential in establishing a diagnosis, is precluded by marked physical and mental deterioration of the patient.

Careful general examination should be conducted in all cases in which there is a clinical picture of tumor of the brain. Any unusual clinical or laboratory observations should be investigated further. Thus at times, by the use of the bronchoscope, proctoscope or cystoscope, it is possible to demonstrate a malignant lesion outside of the central nervous system and thus probably to save the patient from an unnecessary and hopeless operation on the brain.

Roentgenograms of the head and thorax should be made as a routine in

all cases in which tumor of the brain is suspected. There was pulmonary involvement, either of a primary or of a secondary nature, in 83 per cent of cases in this series in which necropsy was performed. Definite roentgenologic evidence of pulmonary disease was present in 51 per cent of these cases. However, in half of these cases the mistaken diagnosis of inflammatory lesion was made. Shelden has pointed out that, in searching for evidence of a primary malignant tumor outside of the central nervous system, such roentgenologic reports as healed tuberculous lesion, miliary tuberculosis, pleural adhesions, pleural effusions and pneumoconiosis should be received with suspicious reserve, and that re-examination should be made at frequent intervals to determine whether the signs are constant.

If possible, microscopic examination of tissue removed at operation in recent years should be made. Biopsy of enlarged lymph nodes, or of nodules in the skin, may disclose evidence of an extracerebral malignant tumor.

Tumor cells occasionally have been found in the spinal fluid, as in the cases of Schwarz and Bertels, Panton, Stadelmann and Meyer.

Frequently, the general appearance of the patient may furnish a clue to the diagnosis, especially if he is within the usual cancer age, if he has lost appreciable weight, or if he is at all anemic or cachectic. The usual history in a case of metastatic malignant tumor of the brain is one of precipitate onset and rapid progression of symptoms and signs, dissemination of objective signs due to multiplicity of lesions, and, from day to day, considerable fluctuation in intensity of symp-

toms and signs This picture is frequently augmented by mental disturbance, especially of a confusional type

SUMMARY

The incidence of metastatic tumor of the brain is at least 5 per cent of all tumors of the brain observed at The Mayo Clinic

There are focal (masses) and diffuse (encephalitic) lesions in the brain

The primary malignant tumor was in the lung, breast or kidney in more than 50 per cent of the cases

The primary lesion is frequently silent

Metastatic tumors of the brain often present essentially the same syndrome as primary tumors of the brain

All cases presenting clinical evidence of a tumor of the brain should be studied carefully for evidence of primary malignant tumor outside of the central nervous system

In all cases in which there is clinical evidence of tumor of the brain roentgenograms of the thorax and skull, for evidence of metastasis, should be made as a routine

Choked disks occurred in 40 per cent of the cases of metastatic tumor of the brain

Multiplicity of lesions, and consequent dissemination of signs, may lead to the assumption that the cerebral manifestations are the result of inflammatory disease

Mental symptoms, especially of a stuporous or confusional type, occurred in more than 50 per cent of the cases of metastatic malignant tumor of the brain seen at The Mayo Clinic

The incidence and intensity of mental symptoms in this series of cases appeared to bear some relationship to

the incidence of the encephalitic changes

BIBLIOGRAPHY

- BEERMAN, W F Meningeal carcinomatosis, Jr Am Med Assoc, 1912, lvi, 1437-1439
- BUCHHOLZ Casuistischer Beitrag zur Kenntnis der Carcinome des Central-nervensystems, Monatschr f Psychiat u Neurol 1898, iv, 183-210
- CONIGHI, R Sarcoma metastatiche del Cervello, Note e riv di Psychiat, 1922, x, 299-310
- ELZHOZ Quoted by Spiller and Weisenberg
- EWING, JAMES Neoplastic diseases, 1922, W B Saunders Co, Philadelphia, 1054 pp
- FISCHER, O Zur Kenntnis des multiplen metastatischen Carcinoms des Zentralnervensystems, Jahrb f Psychiat u Neurol, 1905, xxv, 125-140
- FRIED, B M Primary carcinoma of the lungs further study with particular attention to incidence, diagnosis and metastases to the central nervous system, Arch Int Med, 1927, xl, 340-363
- GALLAVARDIN, L, and VARAY, F Etude sur le cancer secondaire du cerveau, du cervelet et la moelle, Rev de méd, 1903, xxiii, 441-449, 561-573
- GLOBUS, J H, and SFLINSKY, H Metastatic tumors of the brain, a clinical study of twelve cases with necropsy, Arch Neurol and Psychiat, 1927, xxv, 481-513
- GRANT, F C Concerning intracranial malignant metastases, Ann Surg, 1926, lxxxi, 635-646
- VAN HASSELT, J A Kankermetastasen in de hersenen, (Carcinomatous metastases in the brain) Nederl tijdschr. v geneesk, 1920, i, 2441
- HASSIN, G B Histopathology of carcinoma of the cerebral meninges, Arch Neurol and Psychiat, 1919, i, 705-716
- HASSIN, G B, and SINCE, H D Histopathology of cerebral carcinoma, Arch Neurol and Psychiat 1922, viii, 155-171
- HITZEMANN, JASON Über die Metastasen maligner Tumoren im Zentralnervengewebe

- vensystem, *Virchow's Arch f path Anat u Physiol*, 1911, ccv, 418-443
- VON HEYDE, and CURSCHMANN Zur Kenntnis der generalisierten metastatischen Karsinose des Centralnervensystems, *Neurol Centralbl*, 1907, xxvi, 172-173
- HUMBERT, G, and ALEXIEF, W Contribution à l'étude de la méningite cancéreuse, étude anatomo-clinique, *Rev. de méd*, 1913, xxxiii, 921-955
- KAUFMANN, E Beitrag zur Statistik und Casuistik metastatischer Tumoren, besonders der Carcinommetastasen im Zentralnervensystems, *Cor-Bl f schweiz Aertze*, 1906, xxxvi, 255-261
- KOLPIN, O Multiple Papillome (Adeno-Carcinome) des Gehirns, *Arch f Psychiat*, 1909, xlv, 595-604
- KRASTING, KARL Beitrag zur Statistik und Kasuistik metastatischer Tumoren, besonders der Carcinommetastasen im Zentralnervensystem, *Ztschr f Krebsforsch*, 1906, iv, 315-379
- LEWIS, N D C An unusual manifestation of metastatic miliary carcinomatosis of the central nervous system, *Am Jr Psychiat*, 1925, v, 171-187
- LILIENFELD, and BENDA Über einen Fall von multipler metastatischer Carcinose der Nerven und der Hirnhäute, *Berl klin Wchnschr*, 1901, xxxviii, 729-736
- LISSAUFR, MAX Zur Kenntniss der Meningitis carcinomatosa, *Deutsch med Wchnschr*, 1911, xxxvii, 16-17
- MAASS, SIEGFRIED Über diffuse Karcinomatose der weichen Hirnhäute, *Arch f Psychiat*, 1913, li, 359-386
- MEYER, E Zur Kenntnis der Carcinometastasen des Zentralnervensystems, insbesondere der diffusen Carcinomatose der weichen Haute, *Arch f. Psychiat*, 1922, lxxvi, 283-305
- MORSE, M E Two cases illustrating the pathological and psychiatric aspects of carcinoma metastases in the central nervous system, *Jr Nerv and Ment Dis*, 1923, lvi, 409-425
- PANTON, P N The detection of malignant cells in body fluids, *Lancet*, 1922, ii, 762
- SCHWARZ, E, and BERTELS, A Über "Meningitis" Carcinomatosa, *Deutsch Ztschr f Nerven*, 1911, xlii, 84-94
- SHELDEN, W D Secondary tumors of the brain, *Jr Am Med Assoc*, 1926, lxxxvii, 650-654
- SIEFERT, ERNST Über die multiple Carcinomatose des Centralnervensystems, *Arch f Psychiat*, 1903, xxxvi, 720-761
- SMITH, R P Case of secondary carcinoma of the brain simulating general paralysis of the insane, *Jr. Ment Sci* 1888-1889, xxxiv, 61-65
- SPILLER, W G, and WEISENBERG, T H Carcinoma of the nervous system with the report of eleven cases, *Jr Nerv and Ment Dis* 1906, xxxiii, 500-524
- STADELMANN, E Zur Diagnose der Meningitis carcinomatosa, *Berl klin Wchnschr*, 1908, xlv, 2262-2263
- WALSHE, F M R A case of secondary carcinomatous infiltration of the pia-arachnoid of the brain, presenting exclusively ocular symptoms during life; meningitis carcinomatosa, *Brit Jr Ophth*, 1923, vii, 113-123

Ephedrine in the Treatment of Narcolepsy*

By HARRY A. COLLINS, M.D., F.A.C.P., *Des Moines, Ia*

Cases of narcolepsy of various types have been described in the literature but no successful form of treatment had been recorded until Doyle's¹² recent report. In five cases of this disease the somnolent and cataleptic seizures were abolished within twenty-four hours by the use of ephedrine. In this paper I wish to present two other cases in which I have used this drug with the same success.

The first physician to write upon the subject of narcolepsy was Aretaeus who, in the first century, wrote two books upon "The Lethargics", Galen also referred to abnormal somnolence and lethargy in his writings. Dana¹ was able to find but fifty cases reported prior to 1878. Narcolepsy was first described by Westphal² in 1877, but was given its name by Gélneau³ in 1880. However, Gélneau credits Caffé⁴ with describing the first case in 1862. Fischer⁵ reported one case in 1878.

Gélneau suggested the name of "narcolepsy" for "a rare neurosis characterized by an imperious sleep of sudden onset and short duration which recurred at more or less frequent intervals". At the present time when we speak of narcolepsy we recognize a distinction between those cases of prolonged somnolence which some of

the earlier writers have reported and the true narcolepsy of today in which the diagnosis is based on two very important points, namely, that the conditions of narcolepsy and cataplexy must co-exist. Several German writers have recognized this distinction as did also Lowenfeld⁶ in 1892, Camp⁷ in 1907, Adie⁸ in 1926, Kinnier Wilson⁹ in 1928, Cave¹⁰ in 1929, and Daniels¹¹ and Doyle¹² in 1930. In 1929, Cave of the Mayo Clinic presented narcolepsy as a definite clinical entity in his group of forty-two cases which was the largest single series reported up to that time. He made the statement, "that narcolepsy is a rare condition is shown by the fact that these forty-two cases represent a total registration of 361,602 patients or one case of narcolepsy in every 8,610 patients."

Narcolepsy may be described as a clinical syndrome which consists first of irresistible attacks of sleep which may occur at any time or in any place, and of variable duration lasting from a few seconds to several hours, and secondly, of cataplectic attacks which are characterized by a sudden transitory loss of muscular tone which is usually precipitated by an emotional stimulus such as laughter, anger, excitement or exertion. During these cataplectic attacks the patient may lose complete power in the skeletal musculature and may fall to the ground in

*Received for publication August 2, 1931.

a perfectly helpless condition but in the majority of cases complete consciousness is maintained. These attacks are usually of short duration and following them the patient will be able to continue whatever he was doing before the attack. Occasionally he will merely experience the "shaky spell" without the precipitate fall and at other times only certain muscle groups will be affected rather than the entire muscular system. The narcoleptic and cataplectic attacks usually occur independently of each other. Frequently the patient will refer to the cataplectic symptoms as "shaky spells." He may complain of diplopia and dimness of vision as prodromal symptoms of the attack. Because laughing often precipitates an attack the German writers often refer to it as "lachs Schlag" or "laugh stroke." As Doyle has mentioned, perhaps it is the feeling of mirth rather than the laughter itself which precipitates the loss of muscular tonus. The disease is idiopathic but similar symptoms are not uncommonly associated with inflammatory or neoplastic diseases of the third ventricle.

Pathological changes which may occur in idiopathic narcolepsy have not yet been demonstrated. Somnolence has been noted for a long time as being associated with organic lesions at the base of the brain. As Cave has stated, the sleep of the narcoleptic patient is of a far different type than that of a patient with organic disease of the brain. Fulton and Bailly¹³ were of the opinion, after an extensive review of the subject, that sleep disturbance was the result of changes in the region of the gray matter near the Sylvian aqueduct. We may conclude from this and other data that narcolepsy is the re-

sult of a lesion in the region of the posterior portion of the third ventricle.

The etiological factors of narcolepsy are not known. It has been suggested that encephalitis, so common after the influenzal epidemic of 1918, might be a contributing factor. In Cave's series of cases, twenty-four out of the forty-two patients gave no history of encephalitis. Six of his cases were definitely post-encephalitic, and in twelve of them there was a history of influenza on an average of five years previous to the onset of the narcoleptic symptoms. It would seem, however, that narcolepsy has become much more common since the influenzal epidemic of 1918. Adie²⁴ was of the opinion that the family and personal history of the patient revealed no factors of etiological importance after reviewing fifty cases in 1930. Cave was of the same opinion. Camp, however, thought that it must be regarded as a mental defect. Gelineau speaks of it as a rare neurosis. Purves-Stewart,¹⁴ Church and Peterson,¹⁵ and others have been of the opinion that narcolepsy is hysterical in nature. I believe that narcolepsy cannot be explained on a functional or hysterical basis.

In Camp's series the sexes were equally affected and the age of onset was from ten to fifty-one years. In Cave's series thirty-four cases were in males and eight in females, a proportion of about four males to one female. The age of onset in males varied from nine to forty-six years. The duration of symptoms in males before examination by Cave varied from six months to twenty-one years. The age of onset in females varied from eight to thirty-seven years.

In 1907, Camp was of the opinion

that genuine cases of narcolepsy were not common in the literature. Adie, in 1926, stated that narcolepsy cannot be considered a rare disease. Cave's paper shows rather conclusively that it is a relatively rare condition when only one case is found in every 8,610 patients who were examined at the Mayo Clinic.

Cave's etiologic classification follows:

Idiopathic	23
After encephalitis	5
After infections other than encephalitis	3
Associated with hypothalamic syndrome	4
Associated with sleep attacks only	7
Total	42

Narcolepsy is essentially a chronic disease but the duration of the symptoms is unknown. Cave mentions four cases in which the patients had had attacks of sleep for fifteen, twenty and twenty-three years. Adie states that complete permanent recovery has not been observed.

Cases which often have been confused with true narcolepsy are those of hysteria, epilepsy, encephalitis, hypnosis, brain tumors, cerebral and arterial sclerosis, hypothalamic lesions and the somnolent symptoms sometimes observed in obesity and in pregnant women.

The report on the two cases of narcolepsy examined and treated by me follows:

CASE REPORTS

Case 1. A white male single 34 years of age, was examined on November 15, 1928. His family history was not significant. He had had the ordinary diseases of childhood. When I first saw the patient his present complaint was that of sleeping spells. He had been well in every way until 1918 when

he was in the army and noticed that while drilling he would become very tired. As time went on he would fall over while drilling because of extreme weakness in his muscles. When he went in for mess at noon he would fall asleep and it was with the greatest difficulty that the sergeant could awaken him for afternoon duty. These sleeping spells increased in frequency and severity and his weak spells became more marked on exertion. He said that at times he would sink to the ground if he laughed or became excited. About two months after his trouble first started he was removed to a Government hospital where he was treated for a supposedly weak heart. At no time did he have any dyspnea or edema and he was not conscious of any heart trouble. As time progressed, he often fell asleep while eating, walking and driving a car. His general health remained very good. During the past few years this patient has carried on a gainful occupation as an insurance salesman but it has not been infrequently that he would fall asleep while talking to a client. He has had several automobile accidents lately as a result of falling asleep while driving and he said that it was not unusual for him to fall asleep while driving or walking home and to awaken when he was several blocks beyond his home. His sleeping spells will last for about half an hour and are usually preceded by a drooping of the eyelids and some dimness of vision. His narcoleptic sleep has been very deep and has been as common in the early part of the day as in the latter part. He has had very sordid and wild dreams shortly after going to sleep at night. He often thinks that snakes and mice are crawling about him and while asleep he will even pick mice from his body and insist that those near him take them from his hand. He resents being awakened from the dream state and it has been somewhat pugnacious. He often dreams that the telephone is ringing and gets up to answer it. Since the onset of his trouble he has been unable to sit still, to move without sleeping during the day. His performance and of late it has not been possible for him to drive a car at night.

The sleeping spells as he calls them have continued to trouble him for several years.

Laughter, excitement, anger or any emotional stimulus will bring on a shaky spell and if he is not able to grasp something he will sink to the ground. He has purposely avoided playing billiards because of these spells. The loss of muscular tonus or weakness is of very short duration in his case.

The patient's general physical examination was essentially negative except that he was slightly overweight and appeared to be somewhat dull. His eyelids drooped slightly. He answered questions with dispatch and there was no evidence of any neurotic tendency. He seemed to be ambitious and was very anxious to carry on his work. His blood pressure was systolic 140, diastolic 80, pulse 72, temperature 98.6°. The pupils were regular and reacted to light and accommodation. He has a small adenoma of the thyroid. His heart was normal in size, regular and the heart beats were of good volume. Examination of the lungs was negative. Abdominal and rectal examinations were of no importance. Neurological examination was negative. The fundus examination revealed nothing of significance and x-rays of the skull were normal. The urinalysis showed the specific gravity to be 1022, an acid reaction, no albumin, and no sugar, casts or blood. His blood count showed a hemoglobin of 80 per cent with a red cell count of 4,000,000 and a leucocyte count of 7,000. His metabolic rate was minus twenty on one occasion and minus eighteen on another. A Wassermann reaction was negative.

A diagnosis of idiopathic narcolepsy was made and the following treatment was instituted when the patient was first seen by me in 1928. He was given desiccated thyroid, grains 1 to 2, t i d, large amounts of coffee, and caffeine citrate, grains 15 to 2, t i d. He received absolutely no benefit from this treatment. Midway rest periods and sleep were tried and he would feel somewhat refreshed after these naps but for a short time only. As a matter of fact, the patient's symptoms have remained practically the same and his general health has not been impaired in any way since I first saw him in 1928.

In November, 1930, following the suggestion of J. B. Doyle of the Mayo Clinic, I started to use ephedrine for this disease

entity. At the beginning of this treatment this patient's blood pressure, weight, blood count, urinalysis, fundus examination and neurological check-up were essentially the same as when I first examined him in 1928. His metabolic rate was minus seven which was somewhat higher than the previous tests.

This patient was given 0.375 grain (0.025 gm) of ephedrine on November tenth at five in the afternoon and 0.375 grain (0.025 gm) at eight the following morning, at noon, and at four in the afternoon each day thereafter. Following his initial dose of the drug he drove his car for one hundred and fifty miles on a hunting trip against the wishes of some of his close friends who were afraid that he would fall asleep and swerve the car into the ditch. He stated that he did not have the slightest desire to sleep and was much more awake than anyone else in the party. He had not been able to drive a car at night for several years. He hunted all of the next day, walked a great deal, but had no sleepy or weak spells. He returned home on the following day and spent the morning working on his car, had his noonday lunch, read in the afternoon and attended a "movie" that night. He had no desire to sleep during the "movie."

This patient has continued to be symptom-free from both his narcoleptic and cataleptic spells. It is interesting to note that several days after he started the ephedrine he was required to drive to a nearby town about sixty miles distant. As he left the house he picked up a box which he supposed contained his medicine. When it was time for the noonday dose of ephedrine he opened the box and found that he had brought the wrong medicine along. He attempted to purchase some ephedrine but it could not be obtained. As a result he was forced to go without his medicine until he returned home that night. He got along fairly well in the early afternoon but stated that he had to pull off the road several times on the way home to sleep for ten or fifteen minutes. He has played billiards without any trouble and says that his night sleep has been much more restful and that he does not have horrible dreams as before.

I still have this patient under observation and it has been necessary to increase the

dosage of ephedrine from 0.375 gr (0.025 gm) three times a day to 0.75 gr (0.05 gm) three times a day in order to keep the patient symptom-free.

Case II Is that of a boy, 13 years of age, who is perhaps overdeveloped mentally and physically for his age. He reported for examination on November 13, 1930, complaining of sleeping spells since the age of eleven years. These attacks were first noticed while he was riding in an automobile. As time progressed, he would fall asleep while in school or while eating. The spell would last for fifteen minutes to half an hour and he would be somewhat refreshed when he awakened. His night sleep was restless, he had sordid dreams and it was not unusual for him to get out of bed and walk about. His parents noticed that the weak spells in which he would fall to the ground were associated with laughter and exertion. After a few seconds or a minute he would be able to get up and would then be apparently normal. He tired easily and could not keep pace with other children of his own age in active play. He got along very well in school and was a leader in his class. His holidays were spent in sleeping for the most part and it was necessary for him to have an hour's sleep at noon each day in order to carry on his school work in the afternoon. It was not difficult to awaken him from his narcoleptic attacks.

The boy's family and personal history was negative. On general examination nothing significant was noted except that he was slightly obese and rather mature both mentally and physically. Basal metabolic reading was minus twenty when taken on two different occasions. His blood count and urinalysis were negative. His blood pressure was 100/80, pulse 72, temperature normal. Neurological examination was negative. The x-ray examination of his skull was negative.

I started treating this patient with ephedrine and he was given 0.375 grain (0.025 gm) of the drug at 7:45 A. M. the same dosage at noon and at 4 P. M. He was greatly relieved of his symptoms but continued to have occasional sleeping spells while riding in a car. He was able to enjoy a good joke and to play a game of football without having an attack or cataplexy. I

increased the dosage of ephedrine to 0.75 grain (0.05 gm) in the morning and at noon, and to 3/75 grain (0.025 gm) at four in the afternoon. He felt even better under this increased dosage but had one or two attacks of narcolepsy while in his manual training class in school and also fell asleep for a very short interval while reading. The medication was then increased to 0.75 grains (0.05 gm) three times daily. He now feels very well, is much more active, his night sleep is more restful, he is entirely free from the cataleptic attacks, and his parents say that they have noticed a remarkable change in the boy. He has had one or two short sleeping attacks.

The symptomatic treatment of narcolepsy has been without results until Daniel's¹¹ and Doyle's¹² recent report in which they suggest the use of ephedrine. Camp⁷ in 1907, Adie⁸ in 1926, Brock¹⁰ in 1928, Pearce¹⁷ in 1928, Cave¹⁰ in 1929, Common¹⁸ in 1929, Levin¹⁰ in 1929, Denyer²⁰ in 1930, and Ziegler²¹ in 1930, all of whom have reported cases of narcolepsy, are agreed that the different forms of treatment which they have used have not been effective. These included desiccated thyroid, caffeine citrate, liquid strychnine, hormone pituitary gland, sedatives, deep roentgen-ray therapy, and regular intervals of rest in bed, the two latter measures having afforded slight relief.

To gain the best results in the treatment of narcolepsy, ephedrine should be given orally in doses ranging from 0.375 grain (0.025 gm) to 0.75 grain (0.05 gm) three times daily. The first dose is best given at eight o'clock in the morning, the second at noon and the last at four in the afternoon. The last dosage is given early because Doyle has found that in some instances when the dosage has been given later in the day it has proved too stimulating.

and the patient has complained of insomnia and restlessness. It has been my experience in the cases that I have treated that the night sleep has been much more restful since the patient has been taking ephedrine and that my patients have been practically free from the morbid dreams that are so frequently a part of the narcoleptic syndrome. I think that it is perhaps most advisable to start these patients on an initial dose of 0.375 grain (0.025 gm) three times daily, and then to gradually increase to 0.75 grain (0.05 gm) three times daily, if necessary. Doyle increased the dosage in one of his cases as high as 1.125 grain (0.73 gm) three times daily, but the dose proved too stimulating for the patient. It appears to be very easy to establish the minimal dosage within a short period of time. There is the possibility that a slightly increased dosage of ephedrine may be required from time to time in these cases. So far as we know, there is no deleterious effect from the use of ephedrine in the amounts mentioned above.

Doyle says that "Chen and Schmidt,²² and Johnston²³ commented on the occurrence of sleeplessness in certain persons following the use of ephedrine. More recently it has become common knowledge that ephedrine tends to abolish the narcotic effect of sodium iso-amylethyl barbiturate (sodium amytal) and that as an antidote to morphine it is more valuable than caffeine."

I feel that Doyle and Daniels deserve great credit for suggesting an apparently successful symptomatic treatment for the symptom complex known as narcolepsy for which, up to

the present time, the medical profession has had nothing whatever to offer.

I believe that more time will be required to observe these patients who have been treated with ephedrine before final conclusions can be reached but so far the results in most instances have been remarkable.

REFERENCES

- ¹DANA, C. L. On morbid drowsiness and somnolence, *Jr Nerv and Ment Dis*, 1884, *ii*, 153-176.
- ²WISTPHAL, E. Berliner Medicinische Psychologische Gesellschaft, *Arch f Psychiat*, 1876, *vii*, 636-656.
- ³GÉLINHAU. De la narcolepsie, *Lanc Franç Gaz des hôp*, 1880, *liii*, 626-628, 635-637.
- ⁴CAFFÉ. *Journal des connaissances médicales pratiques*, Aug 20, 1862 (See reference 3).
- ⁵FISCHER, F. Epileptoide Schlafzustände, *Arch f Psychiat*, 1877, *viii*, 200-203.
- ⁶LOWENTHAL, L. Über hysterische Schlafzustände, deren Beziehungen zur Hypnose und zur grande Hysterie, *Arch f Psychiat*, 1891, *xxii*, 715-738, 1892, 40-69.
- ⁷CAMP, C. D. Morbid sleepiness, *Jr Abnorm Psychol*, 1907-1908, *xi*, 9-21.
- ⁸ADIE, W. J. Idiopathic narcolepsy, a disease sui generis, with remarks on the mechanism of sleep, *Brain*, 1926, *xlix*, 257-306.
- ⁹WILSON, K., and others. Discussion on narcolepsy, *Proc Roy Soc Med*, (Sect Neur), 1928, *xxi*, 37-46.
- ¹⁰CAVE, H. A. Narcolepsy, *Proc Staff Meet Mayo Clin*, 1929, *iv*, 281-284.
- ¹¹DANIELS, L. E. A symptomatic treatment for narcolepsy, *Proc Staff Meet Mayo Clin*, 1930, *v*, 299-300.
- ¹²DOYLE, J. B. Discussion. A symptomatic treatment for narcolepsy, *Proc Staff Meet Mayo Clin*, 1930, *v*, 299-300.
- ¹³FULTON, J. F., and BAILEY, P. Tumors in the region of the third ventricle, their diagnosis and relation to pathological sleep, *Jr Nerv and Ment Dis*, 1929, *lxix*, 261.

- ¹⁴PURVES-STEWART The diagnosis of nervous diseases, 1924, Ed Arnold and Co, London
- ¹⁵CHURCH, A, and PETERSON, F Nervous and mental diseases, 1923, W B Saunders and Co, Philadelphia
- ¹⁶BROCK, S Idiopathic narcolepsy, cataplexia and catalepsy associated with an unusual hallucination, case report, Jr Nerv and Ment Dis, 1928, lxxiii, 583-590
- ¹⁷PEARCE, M G Narcolepsy, Texas State Jr Med, 1928, xxiv, 371-373
- ¹⁸COMMON, G R Narcolepsy following epidemic encephalitis, Jr Am Med Assoc, 1929, xciii, 29-30
- ¹⁹LEVIN, M Narcolepsy, Gelmeau's syndrome and other varieties of morbid somnolence, Arch Neur and Psychiat, 1929, xlii, 1172-1200
- ²⁰DENIER, S E A case of narcolepsy, Brit Med Jr, 1930, i, 1172-1173
- ²¹ZIEGLER, L H Narcolepsy after severe pneumonia, Med Clin North Am, Mayo Clin Vol, 1930, xiii, 1373-1374
- ²²CHEN, K K, and SCHMIDT, C F The action and clinical use of ephedrine, alkaloid isolated from Chinese drug, ma huang, Jr Am Med Assoc, 1926, lxxvii, 836-841
- ²³JOHNSTON, J I The action and clinical use of ephedrine Discussion Jr Am Med Assoc, 1926, lxxvii, 842
- ²⁴ADIE, W J The clinical features of idiopathic narcolepsy Practitioner, 1930, cxvi, 288-295

Typhus-Like (Spotted) Fever from Tick-Bite*

Rocky Mountain Spotted Fever Type; Identified with a Symbiont Proteus-like Septicemia

By NOXON TOOMEY, B A , M D , F A.C P , *Palmyra, Mo*

CONSIDERING their world wide spread, and the toll of life they take annually, the typhus and typhus-like fevers are foremost among the grave fevers about which there is, at present, very little established concerning their microbic origin¹⁶⁷ Consequently, specific therapy for these malignant fevers, so very urgently needed, has remained, and will perhaps continue to remain, contingent for its development upon discovery of more complete and exact facts concerning their microbic origin Therefore, any data, even the least, should be made known in order that the typhus group of diseases may be placed on as complete and as scientific a foundation as the enterioidea group of fevers

Although Rocky Mountain spotted fever has been demonstrated to be a different disease from typhus fever, it should be classed in the typhus group of fevers According to observations by Spencer there is a febrile disease clinically indistinguishable from spotted fever of the Rocky Mountains but caused by a tick-borne virus that is not the virus of Rocky Mountain spotted fever¹⁶⁶ Hence a sporadic case, al-

though clinically indistinguishable from spotted fever of the Rocky Mountains, if originating remotely from an endemic area, and without obvious contact with ticks imported from an infected area, should be classed as a typhus-like fever from tick-bite of Rocky Mountain spotted fever *type* until such time as the virus causing the sporadic case can be positively identified to be that of spotted fever of the Rocky Mountains This identification in our present knowledge can be made only from the patient's fresh blood (drawn during the fastigium of the disease), inoculated into guinea-pigs known to be susceptible to spotted fever, and into others known to be immune to spotted fever As differential immunity tests have not been made with the virus of this case, the case will for the present be referred to as of Rocky Mountain spotted fever *type*, although clinically a typical case of that disease

The purpose of this paper is to describe for the first time a case of Rocky Mountain spotted fever type originating in Missouri, midway between the original endemic area and the recently discovered eastern-southeastern states area,²¹⁷ secondly, to describe for the first time the clinical pathology of the

*Received for publication, July 31, 1931

spinal fluid in a spotted fever, and thirdly, to call attention for the first time to a virus pathogenic for man and maintained in nature probably as an antagonistic symbiont of a proteus-like microorganism.

A bacteriological and immunological study of this case has been prepared as a separate report.

CASE REPORT

Unexpectedly, and under circumstances that made a complete bedside study out of the question, I was called upon to render medical care to a woman who was found, in time, to have a disease which I never would have supposed could come for observation within the locality in which I practice. Although the uncontrollable restrictions of time and the distant location of the patient's residence, made it impossible for me to do certain laboratory work, and to repeat some bedside examinations as often as I would like to have done, the clinical and bacteriological data obtained are of sufficient value to warrant publishing, especially in connection with the recent discovery of Rocky Mountain spotted fever in eastern and south-eastern states, and the hitherto debatable observations concerning the nature of the virus causing spotted fever.^{110 101 102}

The patient's demise, although certified as due to Rocky Mountain spotted fever, should not be interpreted in such absolute terms, as actually the patient had an advanced heart lesion (double mitral—nodal arrhythmia) and died a cardiac death, although in mentioning this fact it is not intended to minimize the severity of the infection, which was gravely prostrating from its onset, and hyperpyrexial after the third day. It has been said that no one over the age of fifty has been known to survive the malignantly virulent form of spotted fever to which this case has closest resemblance.¹

Mrs. F. F., of Union Township, Marion County, Missouri, aged 69 years, 5 mos. housewife of naturally large and robust frame and musculature (known weight 166 lbs.), had resided on a farm practically all of her life and continuously so during the

latter half. She bore three healthy children (no miscarriages) by first marriage. Her second marriage was subsequent to menopause, which was without event. Inured to heavy manual labor up to four or five years ago.

Previous Medical History. Four or five years ago she began to develop an arthritis deformans that involved chiefly the hands and knees with moderate severity and other joints to lesser degree. She had not considered herself habitually constipated prior to four years ago but following a hemorrhoidectomy a year and a half ago whatever degree of constipation there may have been became worse, necessitating the use of a saline cathartic every few days.

Cardiac insufficiency, first noticed about two and one-half years ago became worse and remained so following a "typhopneumonia" about eighteen months ago. "Pneumonia" (in late autumn—diagnosed by osteopath) lasted acutely for four or five weeks, and with convalescence for four months, was said to have been of severe degree, with considerable emaciation (this illness has a bearing on recently finding her serum to agglutinate *B. typhosus* in dilution of 1:80, partial in 1:160).

The patient had otherwise been well except for one attack of acute frontal and ethmoidal sinusitis about ten months ago. Since then she was semi-invalided due to cardiac condition and rheumatoid arthritis but was nevertheless able to do most of her household and garden work the greater part of the time.

Present Illness History of Tick-bite. During the morning of May 29th, 1931, patient walked near wooded hills to inspect some flooded fields in a creek-bottom. Late on the same day a "small, red common wood-tick" was discovered on her right forearm where it had engorged itself, about three centimeters proximal to the fourth metacarpal-phalangeal joint. The tick was removed and destroyed by a grain duster of the experienced animal husbandry. It was identified as a live *D. variabilis* in all respects and distinguished from the tick that was removed November 1930 when the tick was removed from the patient's arm. It was found to be a female, about two per cent. engorged.

the evening of the day following as the site of the tick-bite was then itchy

Incubation Patient continued to feel well for seven and a half days, up to and including June 5, 1931, the afternoon of which day she made a trip to Palmyra, Mo., seven and a half miles distant, returning cheerful and without exceptional fatigue. Some vague malaise ("rheumatism getting worse") was perhaps noticed before retiring on June 5, although she slept the forepart of the night, but only brokenly and with restlessness during the latter part, which for her was quite unusual

Onset The following morning, June 6, Mrs. F. arose at 5 30 A. M. with a dull frontal headache, a pain in the left side of neck, and discomfort through her right hypochondriac region. She milked several cows but as malaise became rapidly worse and a sense of muscular weakness developed, with pronounced dull (deep drawing and boring) pains in extremities, particularly in biceps brachii, flexors of hands, hamstrings and crural muscles, she kept in bed from 6 30 to 8 30 A. M. but again got up and tried to do her housework. About 10 00 A. M. she took to bed with sudden profound chilliness (the day being warm). Chilliness was constant, exceedingly pronounced and was felt about equally over entire body, with absence of 'creepy feelings'. She probably did not have a true rigor but "no amount of bed-clothes and hot water bottles could get her warm". Chilliness continued unabated for four hours and then passed away slowly between 2 00 P. M. and 4 00 P. M. About 5 30 P. M. and again at 6 30 P. M. she vomited (a unique experience for her) and continued to feel nauseated for two hours thereafter. About 7 00 P. M. she had what was thought by relatives to be 'a heart attack' and I was sent for about 7 30 P. M.

Invasion (end of first day) I first saw patient at 8 30 P. M. at which time she answered questions readily, pertinently, coherently, and without retardation. Her temperature was then 102.4° F., pulse 112, respirations 22. Chief complaints were prostration (two days duration), pain in flexor muscles and vaguely in right diaphragmatic region. Slight cough (quite unusual to her) had developed during the latter part of the

day but there was no pain in chest or on deep inspiration, nor sense of thoracic constriction

Initial Physical Examination Eyes, ears, nose and throat were negative, she was edentulous and without struma. Chest was negative, abdomen was not distended nor tender to palpation. No cutaneous lesions except scabbed over tick-bite (to which no significance was attached). Cutaneous tache was without urticarial element but blanching with peripheral erythematization was exceedingly pronounced. Mobility of neck and reflexes were normal. Blood pressure systolic 155 (all beats at 150), diastolic, 108. Hemoglobin, 80 per cent. Heart murmurs were faint and inconclusive but were suggestive of double mitral lesion. Some nodal arrhythmia was present. Heart was transversely enlarged from 4 cm. left of left nipple line to 5 cm. to right of right sternal margin. Patient was slightly obese, tissue turgor was satisfactory.

Initial Impression and Therapy Temperature was tentatively ascribed to nasal sinusitis and subacute cholecystitis or enteritis following constipation and a dietary indiscretion, although a beginning pneumonia was considered possible (due partly to it then being said, somewhat erroneously, that she had had a 'typho-pneumonia' at the same time a year previously). Saline catharsis (effectual at 10 00 P. M.) and a hypnotic (sodium amytal, grains three, every four hours, if necessary) were prescribed, and tincture of digitalis (LaRoche) was commenced in dosage of 24 drops regularly every four hours.

Patient slept for one hour after first dose of sodium amytal but not after second dose, four hours later.

Second Day, June 7th During early morning, restlessness, fever (to 103° F.) and muscular pains having increased, I was called on by her son, and sent by him, sodium salicylate in raspberry elixir, grains twelve, every four hours, with instructions to take patient's temperature every three hours. Temperature continued absolutely constant at 103.2° F. during the second day without improvement in subjective symptoms. Patient coughed occasionally without difficulty, a little thin, clear mucus being

brought up. She cared for no nourishment but took orangeade and lemonade during afternoon without emesis. She slept not at all that night despite sodium amytal grains three every three hours.

Third Day, June 8th Early in the morning I was called to the farm immediately following a sudden change for the worse observed about 6:30 A. M., or about 48 hours after onset of the disease. I found patient stuporous although arousable, but unable to articulate answers to questions which she seemed to understand, and wished to answer to priest and myself. On command she could not protrude her tongue. At that time temperature was 103.6° F., pulse 98, respirations 24. Leucocyte count was 11,000. Fluids, no longer taken through glass tube, had to be fed to her with a spoon, but were swallowed with some slight difficulty.

Description of Skin Lesion At that time, 7:30 A. M., patient was observed to have over her lower limbs, flanks, and forearms (including wrists and backs of hands) a rash of medium profuseness, stated by relatives to have been first observed by them about 5:30 A. M., which would have placed its appearance about 48 hours after onset of the disease. When first observed by me on lower limbs and forearms there was over abdomen, chest and back an evanescent marmoraceousness which before long gave place to pinhead sized macules of dull ham (tawney) color that in a few minutes increased in size and remained permanently. After an hour or so the lesions became progressively more cyanotic or mulberry colored as they increased in size.

Skin lesions were mostly discrete oval or ovoid, split pea to lentil sized, compressible (to fawn color through diascopy) and non-indurated macules, for most part being not raised or only slightly raised above skin level. The macules, irregularly distributed and very slightly morbilliform had their long axes paralleling the cleavage lines of the skin. The color became a dull mulberry red at times but usually was more cyanotic (violaceous) and never was as intense and as red as in meningococcus meningitis. For brief periods the rash lightened to a faint cyanotic hue but never disappeared entirely.

The rash spread upward over abdomen, chest and back during the course of the morning and new lesions appeared on the extremities but the neck and face were at all times spared except for a dusky blush over forehead. The face was then a little puffed and had a lemon tinge over malar eminences but no icterus was visible in the conjunctivae.

The conjunctivae were then very pronouncedly injected, and remained so throughout the third day, but lachrymation was not present. Photophobia pretty certainly was present but on account of the woman's stupor it was not an outstanding symptom. The tongue was moist, a trifle swollen and lightly covered with a white coat down the center. The pharynx was spottily injected and the patient continued to cough at intervals of a half hour or so, but no macular lesions were observed on the palate or buccal surfaces.

As patient had not voided for over twelve hours, and apparently could not do so she was catheterized every twelve hours 800 cc being drawn off the first time but the subsequent amounts diminishing by about one hundred cc each time. The results of urine analysis and other laboratory work will be described following history.

Although patient was always a trifle evanescant, her chest continued without evidence of pleurisy or pulmonary consolidation which with the low white count, stupor and spotted eruption, made me wish to exclude cerebro-spinal meningitis, despite the then well marked clinical picture of typhus fever.

The temperature curve, which from the first had continuously risen without a remission of more than 0.2° F. to a plateau of 103.6° during first half of third day, rose to 104° (axillary) during the afternoon (104.2° in early evening) of the third day, despite more or less constant cool sponging or upper two-thirds of body. Temperature (taken since morning by axilla) was charted at hourly intervals and showed a drop of 102° at 11 P. M. towards close of third day but during night rose to 104° at 5 A. M.

Medication during the third day consisted of tincture of digitalis increased to drops thirty-two every four hours, and a cathartic for morbidly hyperintestined bowels consisting about twice per day of castor oil.

cylate in ten ounces of water given in teaspoonful drenches at five to ten minute intervals, patient then being no longer able to swallow without difficulty

When seen by me at 10 P M towards the end of the third day of disease, pulse was slower (84) and stronger, respirations 22, regular, of good excursion and without difficulty but with faintly audible inspiratory and expiratory wheeze. The patient was still coughing occasionally, but less frequently, chest negative for areas of consolidation (including posterior bases). Temperature 103.6° dropped to 102.2° an hour later, as mentioned above.

A daughter residing at a remote distance, who arrived at 7 00 P M was unquestionably recognized by patient who could not, however, be aroused from stupor easily, nor kept aroused for more than fifteen seconds at a time. Occasionally the patient tried to give expression to some discomfort in lower extremities but was unable to make coherent sounds or gestures, or to turn herself in bed. A coughing spell caused patient to void a little urine, expel flatus and soil herself with a small amount of semi-solid feces (having previously done so about two hours before). Abdomen was neither scaphoid nor distended, flatus having been passed during coughing spells. Spleen was palpable, firm but not hard, and extended four fingers breadth below costal angle.

Sodium amytal (about grains five floated on water) was later reported to have quieted patient a little during the third night.

Fourth Day, June 9th, patient had a 'sinking spell' in early morning and I was summoned to house. At 8 A M temperature was 103.4° (axillary), pulse 82, respirations 22. Pulse was weak but regular. Oxygen with oxygen-carbon dioxide rebreathing revived heart action. Injection of conjunctivae was noticed to have passed away almost completely. Stupor was deeper, patient being not fully arousable, but no evidence of delirium. Flexion of neck restricted but not rigid; patient habitually rolled head to left side. She moved arms with apparent vague purposefulness but ineffectually. Cried out faintly as though in pain when moved, catheterized, and given bed care.

The pulse having been revived, the morning was devoted to lumbar puncture, bedside laboratory work, and practically continuous cool sponging, the digitalis being continued.

Telegraphic request for Rocky Mountain spotted fever vaccine was made to the Secretary of the Montana State Board of Health but Dr W F Cogswell promptly telegraphed back that vaccine was not used therapeutically.

During the fourth day the skin became cool and clammy and the tissue turgor very much reduced. Cough abated and swallowing became almost impossible.

Later Aspects of the Rash. The rash during the fourth day became somewhat confluent in a few places on the back, buttocks, and lower lateral aspects of thorax, abdomen and hips, but nowhere did the blotches exceed an area of one by two centimeters. Interstitial (purpuric) hemorrhage to a grossly noticeable degree was observable in not over ten lesions, chiefly on the distal portions of the flexor surfaces of the extremities. Neither confluence nor purpura were, on the whole, striking characteristics of the rash.

A few new lesions may have appeared during the fourth day but if they did so they did not attract notice.

Not all of the lesions increased in size during the fourth day but after twenty-four to thirty-six hours from the appearance of the rash there was a larger proportion of lenticular and large lenticular lesions than during the day before, the spots being more distinctly visible at a distance, and permanently a more livid blue. Towards the latter part of the fourth day most of the macules were slightly sunk below the general level of the skin, and most of them (except in dependent portions) towards the end of the day took on an ashen blue, 'washed out' appearance.

When patient was seen by me at 10 00 P M the pulse was found to be 136 and thready, the temperature having fallen to 102.6°. The patient was breathing without much difficulty, rate 24, but tracheal rattle was present. Venipuncture was attempted but only 16 c c of blood was obtained due to collapsed condition of veins. During the

night the pulse became imperceptible and patient expired at 7 20 A M on the morning of the fifth day, or about ninety-six hours after onset of definite symptoms of malaise, or about one hundred and eight hours from first prodromata

The temperature readings (axillary) of the last twenty-four hours were as follows: June 9, 6 00 A M, 103.4°, 6 35 A M, 103°, 10 00 A M, 103°, 11 30 A M, 103.6°, 2 35 P M, 103°, 3 30 P M, 104.4°, 5 10 P M, 105°, 5 40 P M, 104.4°, 6 25 P M, 104.2°, 7 00 P M, 103.8°, 8 10 P M, 104°, 9 00 P M, 103.8°, 10 00 P M, 102.6°, 11 00 P M, 102.8°, midnight, 102.8°, June 10, 1 30 A M, 103°, 2 15 A M, 103°, 3 00 A M, 103.4°, 4 00 A M, 104°, 5 00 A M, 104.8°, 6 00 A M, 104.8°, 7 00 A M, 103.6°, exitus at 7 20 A M

Laboratory Examinations

Blood White cell counts at 12 hrs after onset, 11,000, at 48 hours, 11,200, at 72 hours, 7,300 **White cell morphology** (72 hours) Cells took Wright's stain well, cytoplasm staining somewhat more intensely bluish than normal. Numerous polymorphs were quite large due to increased cytoplasm, and were somewhat ameboid in outline, but no polymorph or large mononuclear was found to have cell inclusions except rarely a few polar staining bacilli of Proteus type as described more fully in accompanying section on bacteriology. Although frequently it seemed as though the bacilli were in the leucocytes, in the majority of instances they were lying on the outside of the leucocytes

dilution of 1 80, partial in 1 160 (See history in regard to typhoid fever 18 months previously.) A typhoid agglutination made from partially dried, diluted serum drawn about the same time as that submitted to the National Institute of Health was reported negative by St Elizabeth's Hospital, Hannibal. Agglutination tests were made on blood drawn at the 88th hour of the disease.

Organisms Proteus-like organisms were first observed in the blood 48 hours after onset but no significance was attached to them as they were considered contaminations from the finger although the latter had been well washed with alcohol. Minute diplobacillary (and diplococcoid) organisms were observed in fresh and stained specimens of blood drawn 76 hours after onset, and a few proteus-like organisms were also observed as on the preceding day. Similar organisms having been found at the same time in the spinal fluid (microscopically free from more than a very occasional isolated red blood cell) some attention was paid to looking for granules and motile organisms but none were accepted as being motile (Brownian movement being taken into consideration) during the few minutes then at my disposal for such examination. Subsequent experience has convinced me, however, that there were minute motile (bacillary and diplobacillary) organisms then present. More numerous diplococci were found then than on the previous occasion.

Blood drawn under the most rigid aseptic precautions at the 88th hour of disease (10 hours before death) was sealed in sterile

Differential counts	Baso	Eos	Jung	Stabs	Segments	Lymph	1. Mono
at 48 hrs after onset	0	0	3%	7%	61%	20%	9%
at 76 hrs after onset	0	0	5%	8%	56%	20%	11%

Red cell counts at 7th hour 4 100 000. Color index 1. **Hemoglobin** 80 per cent (Talquist). **Clotting time** (needle drag method) at 48th hour, 275 mm, at 76th hour, 45 mm, at 88th hour 825 mm, with serum deeply tinged with hemoglobin.

Agglutination tests (National Institute of Health—letter of June 15 1931 by R. E. Dyer) Agglutination of *B. proteus* A₁ positive in dilution of 1 20 partial in 1 40. Agglutination of *B. typhosus* positive in

tubes (kept at room temperature about 62 F) and examined fourteen hours later, at which time the blood was found to harbor mature motile proteus-like organisms also numerous minute diplobacilli (protection-like) organisms as well as diplococci and retractile granules. The latter were of all sizes due to the diplococci being bacilli although some granules were observed adherent to the cells. It was thus clear that the organisms were

refractile it was not clear whether they were monococcal forms of the diplococci or the granules associated with the latter. The mature proteus-like organisms were too motile to determine whether any granules were adherent to them, but a close study of stained blood smears indicated that these granular bodies must unquestionably have been within their surface tension area when they were motile. At that time I was not familiar with the work of Ricketts, Wolbach, Cowdry, Nagayo and others, and was disposed to regard the granules as "blood dust" and the proteus-like organisms as a terminal invader. However, subsequent studies, forming the basis of a bacteriological report to be made shortly, have convinced me that the "granules" in all probability constitute the virus of Rocky Mountain spotted fever.

Erythrocyte Morphology Unstained thick whole, thin whole, dry films, and unstained moist chamber films were examined as well as dried films stained with Giemsa's stain and with Wright's stain, Gram's stain, polychrome methylene blue, etc. Several hours search under the oil immersion ($\times 1100$) permitted drawing the conclusion that no organism could be found within the erythrocytes. The same basal (chromatin) staining, ultramicroscopic granules (monococci?) could be found in relation to the periphery of the red blood cells as mentioned above for the proteus-like organisms. In most instances the granules, which were a little angular in outline (wedge-shaped) appeared to be in contact with the surface of the erythrocytes, they were mostly nonmotile, but once a granule was seen to have a changing relation with respect to the erythrocyte, whether this was due to movement of a current in the moist chamber, or to motility originating in the granule, it was impossible to tell.

Stipple-celled degeneration, anisocytosis, poikilocytosis, fragmentation etc., were not observed up to the 88th hour. The sedimentation time was not observed.

Cerebrospinal Fluid Lumbar puncture (at 76th hour of disease). Small amount (6 cc) of fluid was obtained unmixed with the least macroscopic trace of blood. Spinal fluid was under no increased pressure and

came away only by drops at three or four second intervals. Crystal clear as drawn into sterile bottle and sealed.

Cell count, on blood counting chamber numerous fields were examined and averaged at 53 cells per c mm.

Reducing substance absent (0.5 cc used), boiled in three times the amount of Benedict's qualitative test solution. **Albumin** increased. Amount roughly estimated to be three of four times normal. **Globulin**, Pandy's test, not increased.

Red blood cells very occasional (under one to a field). Hemorrhagic encephalitis definitely excluded.

Organisms In fresh spinal fluid used for making the cell count a few proteus-like and di-coccal organisms were observed under high power objective, but no diplobacilli. However, what attracted my attention were groups of exceedingly minute, barely visible, refractile granules too dispersed to constitute even a pseudo-morula, yet suggesting a community. The granules were not entirely scattered at random but all granules could not be associated with groups. When fresh cerebrospinal fluid was examined under the oil immersion ($\times 1100$) these granules were found to vary in size by about 100 per cent in diameter from smallest to largest, the largest being less than half the diameter of the di-coccal (or diplococcal) phase of the proteus-like organism. The granules were not mobile nor was there noticeable movement of or within the colony, which resembled the appearance of a constellation of stars on a bright night.

Fresh cerebrospinal fluid concentrated somewhat by low heat on a bacteriologically clean slide and stained by Wright's and by Giemsa's stain showed numerous mature proteus-like organisms, with polar staining well marked, rickettsia forms in chains of twos and threes, and what appeared to be masses of granular detritus around them. As the latter took the chromatin (polar) staining as well as the polar and band-like masses in the mature proteus-like organisms, the granules were presumed to be bacterial extrusions or nuclear fractions of disintegrated proteus-like organisms. The granules were not pin-point round but had a variable three-cornered rounded angularness or wedge

shape. No micrometer measurements could be made at the time, but the largest granules were estimated not to exceed 0.12 micron in largest diameter.

Urine. Catheterized specimen at 48 hours after onset (12 hr A. M. specimen). Amount, 800 cc. Color, deep amber, colloidal cloudiness becoming flocculent. No bacterial haze, no bile. Sp. gr., 1.022. Reaction acid to litmus. Albumin, large trace. Sugar absent. Microscopically free from pus cells and crystals. Some epithelial cells from bladder.

Catheterized specimen at 72 hours after onset (12 hr A. M. specimen). Amount, 600 cc. Color, dark amber, colloidal cloudiness becoming flocculent. Suggestion of bacterial haze. No bile. Sp. gr. 1.030. Reaction, markedly acid to litmus. Albumin, very small amount. Sugar absent. Microscopically free from pus cells and crystals, epithelial cells from bladder more numerous than on preceding examination. Occasional red blood cells. Numerous motile bacilli now seen for first time, type not identified.

Animal Inoculation

Blood drawn at the 88th hour of the disease and kept sealed in a sterile container at room temperature (62° F.) was injected 22 hrs later into a female guinea-pig. The injection was made at St. Elizabeth's Hospital, Hannibal, Mo., at 8:30 P. M. on June 10, 1931. With sterile syringe 1 cc of patient's (imperfectly clotted) blood was drawn into 2 cc of sterile water and mixed in the syringe and then injected intraperitoneally into a guinea-pig weighing about 220 gms. Only 2.4 cc (0.66 cc of blood) was injected due to plugging of needle. The guinea-pig was found dead about eleven hours later.

When necropsied twelve hours later the guinea-pig was found to have a markedly swollen, erythematous vulva and hemorrhagic foci in all foot-pads of three feet but no cutaneous lesions. The puncture had done no injury to the intestines or to a large blood vessel, and there was no evidence of peritonitis. Several areas of thickly studded 'pin-point granulations' on the parietal and visceral peritoneum were noticed but not at that time realized to be a manifestation of fatal spotted fever in the guinea-pig.

From the small amount of thin, sanguinous fluid in the peritoneal cavity, smears were made and stained with Wright's stain. The smears showed only very occasional proteus-like organisms that took the stain very poorly. It seemed, therefore, likely that these organisms did not proliferate in the guinea-pig, and were not the cause of death.

DIAGNOSIS

Apart from virus studies of this case, preliminarily reported above, the differential clinical study should take into account typhus fever, meningococcus meningitis, typhoid and the paratyphoid fevers, a streptococcus septicemia and spotted fever of the Rocky Mountains. If the fever had been contracted in certain other localities it would be necessary to consider the septicemic type of plague, to say nothing of certain Asiatic and tropical fevers.

The meningococcic and pneumococcic meningitides can be unequivocally excluded by the clear spinal fluid, not under pressure, and the absence of the characteristic and easily recognizable organisms of those diseases.

Typhus fever can not be excluded on clinical evidence alone. Indeed typhus was given serious consideration about the forty-eighth hour after onset, and it was only the history of tick-bite, the more abrupt and quicker more malignant clinical course and profuse lenticular macules (larger and more evanescent than usually occur in typhus) that decided in favor of Rocky Mountain spotted fever. In this connection it is to be noted that *Proteus* V_1 was agglutinated in dilutions of 1:20 and partially in 1:40, but that the Weil-Felix reaction is known to occur in Rocky Mountain spotted fever.

Streptococcic septicemias of malignant character have occurred in my practice and have, of course, been noted to cause petechial eruptions, but the febrile course has always been very irregularly remittent (septic type) and the peliosis has been hemorrhagic (purpuric) from the instant of first appearance, especially never fading under the diascop. Besides, the petechiae come out only in small numbers at a time, at random, the face and neck not being spared and the spread of the eruption is not rapid and orderly like an exanthem, as in spotted fever.

Typhoid fever with typhus-like course occurs occasionally and a case of such sort could not be unequivocally excluded by clinical appearance alone. Also is to be noted that the patient's serum was reported to have agglutinated *B. typhosus* in dilution of 1:80 (partial in 1:160) although by one observer it was reported negative in blood drawn at same time as that from which the quasipositive report was obtained. In this connection is to be observed that the patient probably had a case of typhoid fever about eighteen months previously. The rapid pulse, moist anemic, swollen tongue, firm spleen, absence of abdominal distention and urine without a well marked bacterial haze were not conformable to typhoid fever in even an early phase.

Over and above the history of tick-bite, and the virus (with a rickettsia-like phase) obtained from the blood and spinal fluid, the character of onset, steadily rising unremitting fever, very pronounced injection of the conjunctivae without lacrimation, and the typical muscle pains associated with the type of eruption would be sufficient to

establish a clinical diagnosis of Rocky Mountain spotted fever.

For the history, symptomatology and clinical types of Rocky Mountain spotted fever see the author's paper "Mountain Fever and Spotted Fever of the Rocky Mountains—Clinical Studies"

BRIEF CORRELATION WITH PREVIOUS INVESTIGATIONS

Spotted fever of the Rocky Mountains was first described clinically in 1896.¹ Clinical differences between the virulent form in the Bitter Root Valley and the more benign form in Idaho were described between 1898 and 1902.^{2,3,6,14} An intermittent form, very probably however a separate disease, was described by Kieffer in 1907.³⁵

Wilson and Chowning focussed attention on the transmission by a tick,⁵ but mistook artifacts for proplasmids.²⁷ Anderson supported the tick theory and found in the blood, during the disease, diplococcoid organisms that resembled forms encountered by me.¹¹ Stiles, who had attacked the tick theory in 1905,²² described the common vector, *Deimacentor andersoni*, in 1908.⁴² McCalla and Biereton in 1905 transmitted the disease by tick-bite to man,³⁷ and in 1906 King²⁴ and Ricketts²⁰ transmitted the disease by tick-bite to guinea-pigs.

Chowning in 1908⁵⁴ described, as the cause of the disease, but on inconclusive evidence, a proteus-like organism similar to the one recovered by me and shown by me to be non-pathogenic.

Ricketts succeeded in maintaining the virus in the guinea-pig²⁵ and showed that it was non-filterable,³² later confirmed by Spencer and

Parker¹⁴⁵ Ricketts incriminated minute, uncultivable diplobacilli (rickettsiae) which he found were transmitted from one tick generation to the next through the eggs⁵⁵ Moore in 1911 showed that the tick did not infect at once but required 175 hours to infect a guinea-pig and that it required about ten hours of feeding for a tick to acquire infectiousness from a guinea-pig⁷¹ Maver showed that ticks other than *D andersoni* could transmit the disease⁷³

In 1907 wild rodents, which had been suspected as being the natural reservoir of the disease were found to be susceptible to it³³ Studies by McClintic, who lost his life in investigation of this disease, had to do chiefly with the disease in nature and the institution of control measures by clearing underbrush, destroying small wild life, etc⁷⁹

Bacteriological work done by Mitche and Parsons in 1916 showed that the virus could not be recovered by the cultural means then available⁹⁶

On presumptive but very equivocal evidence, Wolbach in 1918 described Rickett's diplobacilli as the virus¹⁰² and obtained some growth of these rickettsiae in tissue cultures¹²⁷ Noguchi later failed to isolate a virulent rickettsia from known infected ticks but did show that three strains of rickettsiae from such ticks were not pathogenic,¹⁶¹ whereas a filter-passing virus could be obtained from *D andersoni*¹⁶²

The most significant recent developments have been the demonstration of the spread of the disease in the Rocky Mountain and adjacent states,¹²⁷⁻²⁰² the development by Spencer and Parker of a practical vaccine from

ground-up infected ticks^{153 169} and their studies of the virus^{145,187} Spencer and Parker showed that the virus has a latent, immunity producing phase and that to acquire virulence it requires reactivation, which occurs during the process of engorgement of the tick¹³⁰ They also showed that the virus was not thrown down by high speed (8800 R P M) centrifugalization, and that it could not be separated from the red corpuscles and white blood cells by repeated washings¹⁵⁵

The most important recent developments have been the discovery of transmission in nature by means of the rabbit-tick,¹³¹ the introduction of tick parasites,¹⁵³ the further demonstration of the utility of the Spencer-Parker vaccine,²⁰⁹ and the demonstration of the disease in an eastern and southeastern states endemic area by L. F. Badger, R. E. Dyer and A. Rumreich^{210 217}

REFERENCES

The numbers indicate the chronological sequence of the articles in a complete bibliography of the disease compiled by the author. All articles were read in the original unless marked NR.

- ¹SWIFT, C. L., SPENCER, W. D., COLLESTER, GEORGE FAIRCHILD, R. M., BOWERS, L. C., DUBOIS, J. K., FICKES, D. W. and ZIMM, H. (through CARL MARSHALL W. WOOD, U. S. A.), Spotted fever as reported from Idaho. Report of the Surgeon-General, U. S. Army for period ending July 1 1895. Wash. D. C., Govt. Print. O. 1896 pp. 60-65.
- ²MANN, EDWARD E. Some observations on the so called spotted fever of Idaho. Med. Sentinel 1899 vii 433-438.
- ³GUTH, DR. Spotted fever in Utah. The Missourian 1912.
- ⁴WILSON, L. B. and CROSS, W. J. The so-called spotted fever of the Rocky Mountains. In Ann. Med. Nat. Hist.

- 1902, xxxix, 131-136, and Northwestern Lancet, 1902, xxii, 410-412
- ⁹MANNING, W. L. Spotted fever in Oregon. Med Sentinel, 1903, xi, 389
- ¹⁰ANDERSON, JOHN F. Spotted fever (tick fever) of the Rocky Mountains. A new disease. Bull No 14, Hyg Lab, U. S. Pub Health and Mar Hosp Serv., Wash., D. C., pp. 1-11
- ¹¹ANDERSON, JOHN F. Spotted fever (tick fever) of the Rocky Mountains. A new disease. Am Med., 1903, vi, 506-508
- ¹²WILSON, L. B., and CHOWNSING, W. M. Studies in *Pyroplasma* *forsteri* ("spotted fever" or "tick fever" of the Rocky Mountains). Jr Infect Dis., 1904, i, 31-57
- ¹³STILES, CHAS. WARREN. A zoological investigation into the cause, transmission and source of Rocky Mountain "spotted fever." Bull No 20, Hyg Lab, U. S. Pub Health and Mar Hosp Serv., Wash., D. C., 1905, 1-121
- ¹⁴KING, W. W. Experimental transmission of Rocky Mountain spotted fever by means of the tick. Preliminary note. Pub Health Rep., U. S. Pub Health and Mar Hosp Serv., 1906, xxi, 863-864
- ¹⁵RICKETTS, H. T. The study of "Rocky Mountain spotted fever" (tick fever?) by means of animal inoculations. A preliminary communication. Jr Am Med Assoc., 1906, xlvii, 33-36
- ¹⁶MAYO, HARRY N. Rocky Mountain or spotted fever. Jr Am Med Assoc., 1906, xlvii, 36, and Med Sentinel, 1906, xiv, 370-371
- ¹⁷RICKETTS, H. T. The transmission of Rocky Mountain spotted fever by the bite of the wood tick (*Dermacentor occidentalis*). Jr Am Med Assoc., 1906, xlvii, 358
- ¹⁸RICKETTS, H. T. Further observations on Rocky Mountain spotted fever and *Dermacentor occidentalis*. Jr Am Med Assoc., 1906, xlvii, 1067-1069
- ¹⁹RICKETTS, H. T. Observations on the virus and means of transmission of Rocky Mountain spotted fever. Jr Infect Dis., 1907, iv, 141-153
- ²⁰RICKETTS, H. T. The rôle of the wood tick (*Dermacentor occidentalis*) in Rocky Mountain spotted fever, and the susceptibility of local animals to this disease. Jr Am Med Assoc., 1907, xlv, 24-27, 127-1281.
- ²¹KILLICK, CHAS. F. Intermitent tick fever. Preliminary report on a new type of fever due to tick bite (Ixodidae). Jr Am Med Assoc., 1907, xlvii, 1154-1158
- ²²MCCARTY, L. P. Direct transmission from man to man of the Rocky Mountain spotted (tick) fever. Med Sentinel, 1908, xxi, 87-88
- ²³STILES, C. W. The common tick (*Dermacentor variator*) of the Butter Root Valley. Pub Health Rep., U. S. Pub Health and Mar Hosp Serv., 1908, xxiii, 949
- ²⁴HARRIS, DE W. P. Rocky Mountain fever. Chicago Med Times, 1908, xli, 272-274
- ²⁵NUMBERS, J. R., HARRISON, J. J., TAYLOR, J. M., et al. (Symposium on spotted fever, Idaho State Medical Assoc.) Med Sentinel, 1908, xxi, 704-711, and Jr Am Med Assoc., 1908, li, 1899-1811
- ²⁶CHOWNSING, W. M. Studies in Rocky Mountain spotted fever. Jr Minnesota Med Assoc and Northwestern Lancet, 1908, xxviii, 45-49
- ²⁷RICKETTS, H. T. A micro-organism which apparently has a specific relationship to Rocky Mountain spotted fever. A preliminary report. Jr Am Med Assoc., 1909, lii, 379-380, 491
- ²⁸MOORE, JOSIAH J. Time relationships of the wood tick in the transmission of Rocky Mountain spotted fever. Jr Infect Dis., 1911, viii, 339-347 (also in Contrib Med Sci, by H. T. Ricketts, Univ of Chicago, 1911, 428-436)
- ²⁹MAVER, MARIA B. Transmission of spotted fever by other than Montana and Idaho ticks. Jr Infect Dis., 1911, viii, 322-326 (Also in Contrib Med Sci by H. T. Ricketts, Univ of Chicago, 1911, 440-444)
- ³⁰MCCLENTIC, THOS. B. Investigations of, and tick eradication in, Rocky Mountain spotted (tick) fever. Pub Health Rep., U. S. Pub Health Serv., 1912, xxvii, 732-760

- ⁹⁶MICHIE, HENRY C, JR, and PARSONS, HOUSTON H Rocky Mountain spotted (tick) fever Report of an investigation in the Bitter Root Valley of Montana Med Rec, 1916, lxxxiv, 265-277
- ¹⁰⁰WOLBACH, S BURT The etiology of Rocky Mountain spotted fever Jr Med Research, 1916, xxxiv, 121-126
- ¹⁰²WOLBACH, S BURT The etiology of Rocky Mountain spotted fever Occurrence of the parasite in the tick Jr Med Research, 1916, xxxv, 147-150
- ¹¹⁹WOLBACH, S BURT Studies on Rocky Mountain spotted fever Jr Med Research, 1919, xli, 1-197
- ¹²⁷WOLBACH, S BURT, and SCHLESINGER, MONROE J The cultivation of the microorganisms of Rocky Mountain spotted fever (*Dermacentor varians rickettsi*) and typhus (*Rickettsia prowazekii*) in tissue plasma cultures Jr Med Research, 1923, xlv, 231-256
- ¹²⁸KELLY, F L Weil-Felix reaction in Rocky Mountain spotted fever Jr Infect Dis, 1923, xxvii, 223-225
- ¹³¹PARKER, R R Transmission of Rocky Mountain spotted fever by the rabbit tick, *Haemaphysalis leporis-palustris*, Packard Am Jr Trop Med, 1923, iii, 39-45
- ¹³⁹SPENCER, R R, and PARKER, R R Rocky Mountain spotted fever Infectivity of fasting and recently fed ticks Pub Health Rep, U S Pub Health Serv, 1923, xxxviii, 333-339
- ¹⁴⁵SPENCER, R R, and PARKER, R R Rocky Mountain spotted fever Viability of the virus in animal tissues Pub Health Rep, U S Pub Health Serv, 1924, xxxix, 55-57, 3027-3040
- ¹⁴⁶PARKER, R R and SPENCER, R R A study of the relationship between the presence of *Rickettsia*-like organisms in tick sinews and the infectiveness of the same ticks Pub Health Rep, U S Pub Health Serv, 1926, xli, 461-469
- ¹⁶⁰SPENCER, R R, and PARKER, R R Rocky Mountain spotted fever Certain characteristics of blood virus Pub Health Rep, U S Pub Health Serv, 1926, xli, 1817-1822
- ¹⁶¹NOGUCHI, H Cultivation of Rickettsia-like microorganisms from the Rocky Mountain spotted fever tick, *Dermacentor andersoni*, Jr Exper Med, xliii, 515-532
- ¹⁶²NOGUCHI, H A filter-passing virus obtained from *Dermacentor andersoni*, Jr Exper Med, 1926, xlv, 1-10
- ¹⁶⁷KUCZYNSKI, M H, and BIELEHNAUM WANDA Die Erreger des Fleck und Felsenfiebers 1926 Berlin, Springer, 256 pp
- ¹⁸³COOLEY, R A Tick Parasites—Executive report 7th Bien Rep Montana St Bd Entomol, 1929, 10-16
- ¹⁸⁸COGSWELL, W F A short review of the work of the United States Public Health Service on Rocky Mountain spotted fever 7th Bien Rep Montana St Bd Entomol, 1929, 69-70
- ¹⁹⁰SPENCER, R R Rocky Mountain Spotted Fever Jr Infect Dis, 1930, xlv, 257-276
- ¹⁹⁷SPENCER, R R, and PARKER, R R Variations in the behavior of the virus Bull No 154, Hyg Lab, U S Pub Health Serv, 1930, 49-60
- ²⁰¹PARKER, R R Present status of the use of public health vaccine for Rocky Mountain spotted fever 8th Bien Rep Montana St Bd Entomol 1931, 36-38
- ²¹⁰BADGER, L F, DYER, R E, and RUMRICH A An infection of the Rocky Mountain spotted fever type Pub Health Rpts, U S Pub Health Serv, 1931, xlv, 463-470
- ²¹⁷RUMRICH, A, DYER, R E, and BADGER L F The Typhus-Rocky Mountain spotted fever group Pub Health Rpts, U S Pub Health Serv 1931 xlv, 470-480

Post-Pneumonic Lung Abscess Resembling Lung Tumor*

With Case Report

By GEORGE F. COOPER, M.D., Lieutenant, Medical Corps,
United States Navy, *Continued, p. 1*

IT IS difficult to differentiate an unresolved pneumonia from an encapsulated empyema in which the retained fluid is under pressure. It is also difficult, at times, to differentiate either of the two conditions mentioned above from a lung tumor. It is usually necessary to take into consideration not only the physical findings and x-ray examination, but the history of onset before an absolute diagnosis can be made.

Middle lobe pneumonia, without involvement of the remainder of the lung, is a rare condition,¹ and may terminate in various ways. It may resolve and clear up in a very short time, or it may go on to suppuration and gangrene. The condition may also break down into abscess formation and this collection of pus be later evacuated into a bronchus and drained. The case reported is believed to be one of the latter type.

It is an unusual case and was variously diagnosed as malignancy, encapsulated empyema, lung abscess, and finally a resolving pneumonia.

Figure 1 shows the first x-ray taken before the pus was evacuated. The

density of the shadow very closely resembles that of a lung tumor. At that time percussion over the area gave a total dullness. Breath sounds were entirely absent. During the night the patient had a series of severe coughing spells and began to expectorate large quantities of a purulent greenish pus which was without the odor usually associated with lung abscess.

The next morning the area was aspirated and nothing could be withdrawn. Another x-ray was taken (figure 2), and it was found that the area in the right lung had changed slightly in density and outline. The top border appeared flattened rather than dome-shape. The patient was then allowed to rest for a few days.

At this time breath sounds were beginning to reappear over the mass, and a third x-ray (figure 3), was made. This latter suggested a resolving pneumonia, with a suggestive area in the center of the mass which resembled cavity formation.

The patient continued to cough up quantities of purulent material for several days, but this gradually decreased in amount and finally disappeared.

During the night in which he first

began to expectorate pus from the lung, his temperature was 103.8° F, but this dropped to 97.6° F, by morning and has been normal since. His leukocytes at that time were 14,600 with 64 per cent polymorphonuclears. Pulse at no time had gone over 100 since day of admission to hospital and respirations had been normal at all times.

Since this patient gave a history of illness with pain in left chest for three months, it is believed that he had a pneumonia at one time which left a collection of pus either in the middle lobe of the right lung, or an encapsulated empyema between the upper and middle lobes.

While the x-ray in figure 1 resembled a pneumonia, the pulse, respiration and leukocyte count were all against such a diagnosis. The mass was sharply outlined and the dullness on percussion such that a diagnosis of malignant tumor seemed justified. The patient's general condition was not good, and he gave a history of having lost considerable weight over a period of three months.

His most constant symptom during that three months was pain. This was



FIG 1 First x-ray taken on January 20, 1931.



FIG 2 X-ray taken on January 27, 1931, showing slight decrease in density and size of area.

so severe that he walked in a bent over position. He had no difficulty in breathing and stated that he noted no fever at any time. He was not coughing at time of onset and had no coughs or colds previously.

Sputum examinations have been consistently negative for acid fast bacilli, the only abnormal finding being many pus cells and two organisms in abundance, one of which resembled *B. influenzae*, and the other a short chain streptococcus. Pneumococci were noted once.

Immediately after expectoration from the lung began to increase, the pain in his chest became less, the patient felt better, began to gain in weight and in a few days was symptom-free. The illustrations are from x-rays taken at different intervals as mentioned and show his condition at the different stages of his illness. The case history and laboratory findings are given in detail below. Chart 1 shows the temperature, pulse, and respiration with the drop in temperature during the night of the twenty-third when the abscess began to expectorate.



FIG 3 X-ray taken on February 6th, 1931, showing considerable decrease in size and density of area in lung, with a suggestion of cavity formation

CASE REPORT

January 19, 1931 P A B, a white male, age 33, well developed and fairly well nourished, admitted to medical ward complaining of severe pain in right side of chest, which he states has been present for three months

Past History This is the third attack of the same condition in the past three months. Has had a continuous temperature with night sweats and coughing in the early morning. Contracted syphilis in 1926, but has had adequate treatment

Family History Father dead at 62, heart disease. Mother dead, cause unknown. Two brothers and one sister living and well. No history of cancer, insanity, or tuberculosis in the family

Physical Examination Eyes, ears, nose and throat negative. Heart negative. Lungs: Coarse râles over areas of both lungs, and areas in right lung suggestive of small cavity formation. Patient is suffering from considerable pain in his chest at present, especially when he coughs. There is an area of dulness over the entire middle lobe, right lung. Examination otherwise negative

X-ray of chest, shows a mass which occupies practically one-half of the right lung (figure 1). While this patient has had syphilis, it is not believed that the condition in his lung is a luetic infection. Kahn test is negative and has been for the past year

Laboratory Data Leukocyte count 11,300, neutrophils, 64%. Red blood count, 3,900,000 Hemoglobin, 70% Urinalysis negative Kahn test negative Sputum negative for acid fast bacilli on several occasions, but shows a few gram-positive diplococci, many short chain streptococci, and an abundance of small bacilli, morphologically resembling *B influenzae*

January 22, 1931 Leukocytes 14,600 Polymorphonuclears, 66%

January 24, 1931 Patient had a severe coughing spell last night and began to expectorate copious amounts of purulent sputum. Temperature dropped during the night. Taken to surgical ward and lung aspirated, but no free pus obtained, probably on account of drainage during the night

January 25, 1931 Temperature has remained down and patient feels much better. Pain is less. Coughs considerable but it is a productive cough. His condition appears to be either a walled-off abscess occupying the entire middle lobe of the right lung, or a malignancy. The x-ray shadow under the fluoroscope is almost as dense as the heart shadow

January 25, 1931 X-ray of this date shows a suggestion of lessened density in the mass with a change in the outline at the top border. The lower border is ragged and appears to be attached to the diaphragm which is higher than normal on that side. Of course, the right side of the diaphragm is normally higher than the left, but this appears to be even more so, and under the



FIG 4 X-ray of chest made February 14, 1931, showing almost complete resolution

fluoroscope, to move with the mass in the lung

Stereoscopic plates show the condition to be very close to the chest wall anteriorly, and close to the surface of the lung

January 26, 1931 Temperature 98.8° F Has slight pain Cough is still productive of much purulent sputum The sputum has no odor as would be expected from a lung abscess Patient has no history of coughs, colds, or other illness prior to the onset of the present condition, the first symptom of which was pain in the chest, three months ago

January 27, 1931 Examination this date shows a lessened density of the area involved with increased breath sounds Mass does not seem so sharply outlined on percussion X-ray taken in standing position at 36 inch

distance shows a decreased density of the area with a beginning resolution in the center, which seems to be clearing up Top border has changed in appearance Instead of a convex border it is now concave Total area is noticeably decreased in size Patient continues to expectorate considerable purulent material Lung at this stage suggests a resolving pneumonia The part of the lung involved corresponds almost exactly with the outline of the middle lobe right lung

January 31, 1931 X-ray of chest shows decrease in density and size of area in right lung, with adhesions downward and towards the hilum

Further questioning of patient as to onset of illness reveals the following information

"At time of onset his bones ached and he

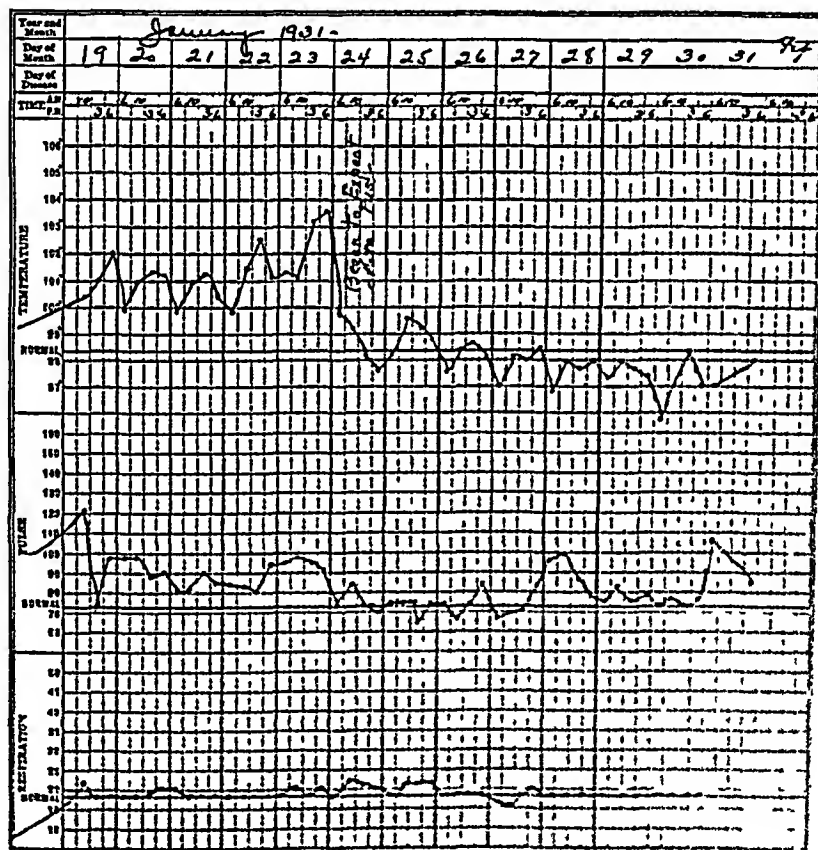


CHART 1 Temperature pulse, and respiration graphs. Note sharp fall in temperature with evacuation of pus by expectoration

felt very weak. His chief complaint was pain even on pressure outside the ribs of his right side. The pain finally became unbearable and he turned in. At that time he had a cough, which was non-productive. He admits that on one occasion, one month prior to admission to hospital, he coughed up considerable pus and all symptoms were relieved for a while.

February 2, 1931. Percussion note is clear and practically the same all over the chest. Auscultation reveals signs of a large cavity with harsh breath sounds. The area over which dulness on percussion was elicited at admission now gives almost cavernous

breath sounds. The remainder of the chest is practically normal.

February 14, 1931. X-ray of chest (figure 4) shows almost complete resolution of the mass and is suggestive of a resolved pneumonia.

April 17, 1931. Guinea pig inoculated with pus from lung on January 27, 1931, is healthy and has gained in weight. Autopsy shows no signs of tuberculosis.

REFERENCE

- WISSLER, and L. JACHES. Clinical roentgenology of disease of the chest, page 233.

Modern Conception of Retinal Detachment with its Relation to Internal Medicine*

By CLYDE A. CLAPP, M.D., *Baltimore, Maryland*

IT MAY seem to you that the question of detachment of the retina is rather a special subject to bring before a group of internists but in recent years there has been a new conception as to the etiology of one type of this condition, and a new line of therapy has been developed. This new conception of etiology and therapy as well as our frequent call upon the internists for help in diagnosis of the cause of these conditions warrants our consideration of this subject.

As you all know the retina is very loosely attached to the underlying tissue and can with comparative ease be separated from it. Detachments from the etiological standpoint are usually grouped under four heads:

- (1) Those due to trauma,
- (2) Those in which the retina is pulled away from its attachment by bands of connective tissue in the vitreous,
- (3) Those in which the retina is pushed from its bed either because of a tumor or growth of the choroid or because of an extensive exudate,
- (4) Those in which no particular

cause can be determined, or the so-called idiopathic group.

Those cases which come under group 1, due to trauma, usually show marked improvement under rest and frequently entirely subside, leaving the retina fully attached and with normal fields of vision.

The cases in group 2, which are caused by contracting bands of fibrous tissue in the vitreous, usually follow a hemorrhage into the vitreous and the treatment is almost universally disappointing.

Group 3, consisting of those cases in which the retina is pushed from its bed is of very great interest. Especially is this true in those cases resulting from massive exudate from the choroid, a condition which occurs in acute toxemia of pregnancy or in acute nephritis not associated with pregnancy.

I will show you two examples of the former, one showing a large detachment above and below and the other showing a complete peripheral detachment. The ophthalmoscopic picture is most striking and when first observed the tendency is to give a very grave prognosis as to sight. One can, however, be very optimistic since practically all of these detachments subside as the general condition improves.

*Presented at the clinical session of the Baltimore Meeting of the American College of Physicians, March 24, 1931, at the Wilmer Clinic.

and the retina becomes fully re-attached. The detachments in acute nephritis have a similar appearance to those of toxemia of pregnancy and both have a tendency to change their appearance very rapidly. My experience has been that when detachments occur as a result of nephritis not associated with pregnancy, the prognosis as to life is very grave and the patient usually dies within a few weeks or months.

Another very small number found in this group are due to a tuberculoma occurring in the choroid, which may elevate the retina. The use of the graduated tuberculin skin test as an assistance in diagnosis is to be recommended and tuberculin therapy is indicated. In a few cases beneficial results are obtained from this line of therapy, although often the pathological process is so advanced that improvement fails to take place.

Group 4, which is by far the most numerous, consists of those detachments which occur spontaneously and which were formerly known as idiopathic. It is to this group that I especially desire to call your attention in view of the new conception in regard to the etiology, and the new treatment instituted. The explanation given by Leber and later adopted by Gonin, that usually there is a localized disease of the retina, with atrophy and at times cystic formation which finally tears, leaving a gap or rent through which the vitreous penetrates, separating the retina from the choroid and giving the

characteristic appearance, is the one widely held at the present time.

I have recently been fortunate in securing an eye which showed an old idiopathic detachment and I have had serial sections made in order to demonstrate, if possible, the presence or absence of such a rent. These sections show an old degenerated retina with marked cystic formation and at a short distance from the ora serrata there is a considerable rent in the retina through which the vitreous has penetrated thereby elevating the retina. This rent is comparatively small since ten sections upon either side shows a continuity of the retina. A similar rent also exists on the opposite side of the eye.

Gonin believed that the reason that results were not obtained in the treatment of these cases was that the opening in the retina allowed the vitreous to penetrate beneath the retina and this prevented its re-attachment. He therefore conceived the idea that if one could close these openings by searing their margins with the actual cautery, the retina would return to its bed. He first reported his results in 1919 and at the present time (July, 1930) claims that sixty per cent of these cases, if the detachment is recent, can be cured by this procedure. While American ophthalmic surgeons are not quite as optimistic as our European colleagues the procedure certainly offers more hope for restoration of vision than the old line of treatment of rest in bed for long periods, with hot packs and sweats.

How to Obtain More Autopsies*

By D SCHUYLER PULFORD, M D , F A C P , *Woodland, California*

THAT the percentage of autopsies obtained in any hospital or community is in direct proportion to the interest and efforts of the physicians in getting post mortems, is proven by numerous experiences. Some institutions and teaching hospitals have an average of eighty per cent, or more. In most city hospitals permits are exceedingly low, say from five per cent to twenty per cent.

Justifiable pride in ninety per cent autopsies obtained at the Woodland Clinic, for institutional deaths during 1930, and a belief that a discussion of the methods used in obtaining such a high percentage of necropsies will be of help to others, prompts the following report.

REPORTED PERCENTAGE OF PERMISSIONS

The Council on Medical Education and Hospitals of the American Medical Association¹ in its report of the essentials in a hospital approved for interns revised to January 1, 1930, states that "inasmuch as the percentage of autopsies has come to be recognized as an index of the educational activi-

ties in a hospital, no institution will be approved for the training of interns which does not have a record of autopsies of at least fifteen per cent." This requirement has not been changed to date.

This Council reported in 1927² after a survey of 538 representative hospitals in the United States, the following percentages of autopsies:

3 hospitals with autopsies from 90 to 100%
2 hospitals with autopsies from 80 to 90%
9 hospitals with autopsies from 70 to 80%
13 hospitals with autopsies from 60 to 70%
8 hospitals with autopsies from 50 to 60%
26 hospitals with autopsies from 40 to 50%
42 hospitals with autopsies from 30 to 40%
91 hospitals with autopsies from 20 to 30%
35 hospitals with autopsies from 15 to 20%
107 hospitals with autopsies from 10 to 15%
122 hospitals with autopsies from 5 to 10%
80 hospitals with autopsies from 1 to 5%
None recorded 0 to 1%

Percentages have probably improved since that date but they are still lamentably low compared to those obtained in foreign countries.

Henry A. Christian³ of Harvard Medical School states, "The number of necropsies obtained on patients dying in the hospital is perhaps the best single index of the professional efficiency of the hospital or the amount of work devoted to the study on patients by members of the staff or the eagerness of the staff to better their teaching ability."

*From the Department of Medicine and Pathology, Woodland Clinic, Woodland, California.

Received for publication November 18, 1931.

Richards⁴ in 1921, reported that in St Luke's Hospital, New York City, one surgical service obtained forty-five per cent autopsies, and one ten per cent, and drew the conclusion that "success in obtaining necropsies depends upon the zeal and interest of the various staffs"

Doctor Bell,⁵ in 1928, reported a high percentage of autopsies in teaching institutions in Minneapolis and stated that "the most important factor in increasing the number of post mortems is to get the physician deeply interested"

Doctor Kingsford,⁶ in reviewing a year's autopsies in teaching institutions in Hanover New Hampshire, reported forty-five autopsies upon sixty-eight deaths, 66.2 per cent. He attributed a rather rapid increase in the number obtained in his institution to the factor of "merely asking permission"

Robertson,⁷ of Rochester, Minnesota, considers "percentage of permissions an index of the scientific spirit of any medical group" He also states that "when the clinical and laboratory staffs know that a serious effort will be made to get post mortem examinations and that they will be obtained in a large percentage of cases, the whole staff is stimulated to more careful work" And he feels that the patients

will thereby be cared for more safely

It seems probable that when hospital staffs become autopsy minded a minimum of 50 per cent autopsies should be obtained by all hospitals

AUTOPSY MATERIAL

Sixty of the sixty-six patients who died at the Woodland Clinic twelve hours or more after admission in 1930 were autopsied. Although as institutional deaths are usually accorded only those patients who die after being in the hospital forty-eight hours or more, we felt that after twelve hours sufficient contact and interest in the clinical course was established to necessitate a post mortem examination to correlate clinical and pathological findings. If we include five cases dying less than twelve hours after admission who were not autopsied, we have seventy-one deaths with sixty autopsies, or 84.5 per cent. Obstetrical service baby deaths are not figured in this report because autopsies were not sought on this service, most of the deaths being due to prematurity. There were some autopsies done on these babies but neither the deaths nor the autopsies are included in these statistics.

Of those deaths occurring less than twelve hours after admission there were two from cerebral hemorrhage.

TABLE 1

	Admissions to Hospital	Per Cent	Deaths	Autopsies	Per Cent Autopsies
Medical	844	17	44	35	79.54
Surgical	1259	55	27	25	92.59
Obstetrical	157	8			
Total	2260	100	71	60	84.5
Patients dying less than 12 hours after admission			5		
Institutional Deaths			66	60	90.90

THE COST OF AUTOPSIES

The idea that necropsies cost too much money for small hospitals to consider is refuted by our experience. Much benefit is derived from a necropsy even if not done by the best pathologist and even if a complete microscopic and bacteriologic study is not made. When performed in a large pathology section of a university or teaching hospital the expense is great because of the complete detail and thoroughness of the work. The expense of an autopsy in Mt Sinai Hospital in New York City in 1930, where four hundred and twenty-seven were done, was reported by Doctor Joseph Turner¹¹ to be ninety-two dollars each. Such a figure is not applicable to the smaller, less pretentious hospitals or clinic, nor is any such expense necessary. One should not imply from this statement that we advocate a poorer type of work. Until such expense can be met we would advise stimulating interest and increasing the percentage of necropsies until more money is available. This may in turn help to put in motion forces that will bring money for more detailed work. It might be helpful to call attention to the point where the expense of the Mt Sinai system, for example, need not be shouldered by the smaller hospital or group of physicians.

At Mt Sinai under the "Direct Charges" are listed

- (1) Pathologist's salary,
 - (2) Morgue space and overhead
 - (3) Morgue keeper,
 - (4) Supplies
- and under "Indirect Charges"
- (1) Time of staff interns and other attendant's expense in getting permission

- (2) Time consumed in the clinical preparation and presentation

The greatest expense is probably the direct charge to the pathologist's salary. In order to reduce this a part-time pathologist may be employed, or a competent pathologist in the vicinity may be paid by the hospital or group of doctors interested for each post mortem done. All the other fixed charges having to deal with the morgue can be eliminated by the full cooperation of the undertaker. Autopsies can be performed as satisfactorily in an undertaking parlor as anywhere else, and gloves, instruments and supplies are often supplied by the undertakers in exchange for the doctor's good will. As to the indirect charge to staff and clinical pathological conferences, this is not to be thought of on a charge basis in a small hospital or city, for the educational element and the added prestige and ability developed by the doctor more than repays each man for his time. As far as the hospital and public are concerned the small expenditure necessary is well worth while, for as Doctor Turner says it is "eventually returned to the contributing public with compound interest in the form of improved practice of medicine in the hands of better trained physicians."

SUMMARY

1. A practical inexpensive method of getting a high percentage of autopsies applicable to almost any community is outlined.

2. Not having a highly paid pathologist available is not a real obstacle.

3. Sixty of the sixty-six patients who died at the Woodland Clinic twelve hours or longer after admission

is modified by increased knowledge gained by postmortems (5) Aid in settling insurance claims. (6) That there is no delay and no extra charge (7) That the high average per cent of autopsies permitted in the past by all classes of people in the best institutions testifies to the procedure being reasonable and proper.

No such interest in obtaining permissions could be kept alive without a strong stimulus and this was delivered in the form of a bimonthly or monthly clinical pathologic conference, fitting their frequency to the amount of material available, and not to any set date. Since it was the custom to have a weekly staff meeting for magazine reviews, reports of meetings or papers in preparation or heard or read elsewhere, it but remained for the pathologist to request the necessary time to present the material available and ready at any routine weekly staff meeting.

It seems best to have the pathologist as leader to present the case history of all deaths. The stimulus needed to induce and maintain interest in the clinicians depends in a large part on the excellence of the pathologist. The case history of the patient who had no autopsy often served to emphasize how important autopsies are, so they were also presented. After discussion by all doctors who saw the patient, gross specimens were shown and then microscopic slides projected. Closing discussion brings out any mistakes in diagnosis, delays or omissions in treatment and remarks as to similar cases seen formerly or elsewhere. Such universal favorable comment has been received from staff members as well

as visiting physicians that it is planned to extend the clinical pathologic conference to include the material removed at the operating table together with the clinical reports of these surgical cases which present interesting tumors or situations.

Clinicians and pathologists alike admit their limitations and failures, for although death is, *per se*, admission of failure of the physician as treatment did not preserve life, yet often the pathologist, too, is at a loss to explain many causes of death, save by such unsatisfactory terms as surgical shock, toxemia, exhaustion, etc.

Those interested in developing logical and plausible points to convince relatives of the value of performing a postmortem should read Emil Bogen's article printed in *Hygeia*, December, 1926. Also a very good detailed article on, "Answers to Layman's Objections to Postmortems", is that of Doctor Ralph Mills,⁹ published in the Bulletin of the American College of Surgeons, of December, 1930. All pathologists and coroners should also familiarize themselves with Schultz's¹⁰ recent article, "The Law of the Dead Human Body".

To summarize, it appears to the writer that the four most important factors in obtaining autopsies, in the order of their significance are (1) obtaining one hundred per cent effort and interest on the part of the doctors concerned, (2) establishing a close personal understanding and trust and friendship between doctor and relatives during the patient's illness, (3) cooperation of the undertakers, (4) creating the proper public sentiment towards postmortems.

THE COST OF AUTOPSIES

The idea that necropsies cost too much money for small hospitals to consider is refuted by our experience. Much benefit is derived from a necropsy even if not done by the best pathologist and even if a complete microscopic and bacteriologic study is not made. When performed in a large pathology section of a university or teaching hospital the expense is great because of the complete detail and thoroughness of the work. The expense of an autopsy in Mt Sinai Hospital in New York City in 1930, where four hundred and twenty-seven were done, was reported by Doctor Joseph Turner¹¹ to be ninety-two dollars each. Such a figure is not applicable to the smaller, less pretentious hospitals or clinic, nor is any such expense necessary. One should not imply from this statement that we advocate a poorer type of work. Until such expense can be met we would advise stimulating interest and increasing the percentage of necropsies until more money is available. This may in turn help to put in motion forces that will bring money for more detailed work. It might be helpful to call attention to the point where the expense of the Mt Sinai system, for example, need not be shouldered by the smaller hospital or group of physicians.

At Mt Sinai under the "Direct Charges" are listed

- (1) Pathologist's salary,
 - (2) Morgue space and overhead
 - (3) Morgue keeper,
 - (4) Supplies,
- and under "Indirect Charges".
- (1) Time of staff interns and other attendants expense in getting permission,

- (2) Time consumed in the clinical preparation and presentation

The greatest expense is probably the direct charge to the pathologist's salary. In order to reduce this a part-time pathologist may be employed, or a competent pathologist in the vicinity may be paid by the hospital or group of doctors interested for each post mortem done. All the other fixed charges having to deal with the morgue can be eliminated by the full cooperation of the undertaker. Autopsies can be performed as satisfactorily in an undertaking parlor as anywhere else, and gloves, instruments and supplies are often supplied by the undertakers in exchange for the doctor's good will. As to the indirect charge to staff and clinical pathological conferences this is not to be thought of on a charge basis in a small hospital or city, for the educational element and the added prestige and ability developed by the doctor more than repays each man for his time. As far as the hospital and public are concerned the small expenditure necessary is well worth while for as Doctor Turner says it is "eventually returned to the contributing public with compound interest in the form of improved practice of medicine in the hands of better trained physicians."

SUMMARY

1 A practical inexpensive method of getting a high percentage of autopsies applicable to almost any community is outlined.

2 Not having a highly paid pathologist available is not a real obstacle.

3 Sixty of the sixty-six patients who died at the Woodland Clinic twelve hours or longer after admission

Editorial

MOTTLED ENAMEL DUE TO FLUORIDE

In the condition known as mottled enamel the teeth are of normal form but present two different types of color change. They may have an opaque paper-white appearance but more frequently are irregularly mottled or stained yellow, brown or even black. The outer glazed enamel surface, Nasmyth's membrane, is present and appears to be normal, except in those cases which are termed 'corroded'. The brown stain can not occur unless the fundamental mottled defect of the enamel is present and may never develop. This alteration in the appearance of the enamel is highly disfiguring and once established cannot be remedied short of a difficult operative procedure. Moreover, practically every child born and reared in an area in which this condition is endemic is certain to have the condition to some degree. Thus the importance of this affliction will readily be appreciated. The Pittsburgh Section of the International Association for Dental Research has recently devoted an entire program to a discussion of the nature, geographical distribution, and cause of mottled enamel.

The occurrence of mottled enamel at and near the town of Bauxite, Arkansas, has been studied by Kempf and McKay*. This community derived its water supply from wells about 255 feet deep. This deep-well water

had a disagreeable alkaline taste, and many of the families continued the use of spring water for drinking. Evidence collected during the examination of school children showed that (1) No cases of the enamel defect antedated the introduction of the deep-well water. (2) The oldest individual having this enamel defect was born about the time that the deep-well water was introduced. (3) All individuals who had used the deep-well water during any considerable period of enamel formation exhibited the defect. (4) No individual whose enamel had developed elsewhere exhibited the defect. (5) Certain individuals who were residents of this community and attended school there, but who actually lived beyond the distribution of the deep-well water and depended upon the original shallow wells, exhibited only normal enamel. Since the enamel of the temporary teeth almost never shows the defect and the calcification of the permanent teeth does not begin, on the average, until about one year after birth, it is evident that maternal nutrition is not even remotely related to the development of mottled enamel. The food supply of this group of people is from a central store with the staple articles produced and manufactured

*KEMPf, GEORGE A. and MCKAY, LEO S. Mottled enamel in a rural population, *Int. Dental Research*, 1952, vol. 12:1-10. (Received in final form July 19, 1952)

elsewhere. Locally grown products are used to some extent, but the diet of those exhibiting the enamel defect was similar in every respect, except as to source of water, to that of those who escaped.

In the town of Benton, about five miles distant from Bauxite, 124 children were examined. Of these, 103 were native to Benton and neighboring communities exclusive of Bauxite and these all showed normal enamel. The remaining 21 had formerly lived at Bauxite for longer or shorter periods. Of 16, who had lived in Bauxite for one year or more, 11 had mottled enamel.

On the strength of the evidence brought out by this study, together with reports of similar experiences elsewhere, it was decided to abandon immediately the deep-well water supply and to use water from the Snake River which was the source of supply of Benton. Oakley, Idaho, had previously abandoned its otherwise satisfactory water supply because of its apparent causal relationship to mottled enamel.

Ordinary methods of water analysis failed to identify the causal agent. While there were marked differences between the waters, these differences were not unlike those found in many other regions in which the native population remains entirely free from this enamel defect regardless of what the source of the water used might be. However, Churchill² reported the dis-

covery of A. W. Petrey, using spectrographic methods, of fluoride in the deep-well water from Bauxite. He subsequently obtained samples of water from Colorado Springs, a well near Kidder, S.D., a well near Ladgerwood, S.D., and Oakley, Idaho,—all localities in which the enamel defect was known to exist. The presence of fluorides was shown definitely in all cases. Quantitative estimation is difficult and is believed to give low values, but by the best method available the fluoride content of these waters was found to range from two parts per million for Colorado Springs to 137 parts per million for the deep-well at Bauxite, Ark. The survey was then broadened to include the water supplies for a number of cities, widely scattered, in which mottled enamel does not occur. Sixteen were found to have fluorides present, but in all cases to an amount less than one part per million.

The prevalence of mottled enamel in St. David, Arizona, was brought to the attention of investigators at the University of Arizona, in 1930 by A. E. Bard, a dentist of Tucson. Upon investigation³ it was found that, with the exception of one family of three children living seven miles south of St. David and the sister-mothers of two other St. David families, every person born and reared in St. David, or coming there at an early age, showed mottling to varying degrees in every permanent tooth. Although

²CHURCHILL, H. V. The occurrence of fluoride in some waters of the United States, Jr. Dental Research, 1932, xii, 141-148. (Reprinted from Industrial and Engineering Chemistry, 1930, Anal. ed., 263.)

³SMITH, M. C., LANE, EDITH, and SMITH, H. V. The cause of mottled enamel, Jr. Dental Research, 1932, xii, 149-159. Also Technical Bull. No. 32, Agricultural Experiment Station, University of Arizona.

mottled enamel was absent from the teeth of domestic animals in St David and had never been described from other endemic foci, the experimental production of mottled enamel in rats, guinea pigs and dogs was attempted. Diets in which calcium and phosphorus were present in deficient amounts, or in disproportion to each other, also those lacking in vitamin D, failed to produce abnormality entirely similar to the characteristic mottled enamel of man. Also, using both normal and abnormal diets, certain animals were given drinking water from St David and a control series received distilled water. No destructive effect of the St David water was noticed when the diet was adequate in all respects. When, however, the diet was deficient enough in itself to produce observable changes in the teeth, all the animals receiving the St David drinking water gave evidence of this interference at an earlier age.

Realizing that the greater rate of growth of the incisors of rats as compared to children might influence the results of the experiment, further series of animals were given St David water which had been concentrated to one-tenth of its original volume. In some instances the water residue was incorporated in the ration. Positive results were now obtained. Even though the diet was adequate in all respects, the enamel of rats receiving residue from St David water quickly lost its translucency and normal yellow pigment, becoming whiter and more opaque than that of litter-mates receiving the same basal ration but with

distilled water. In a month's time, the enamel of the affected animals was not only dull and chalky white in appearance, but also pitted and corroded. The condition produced seemed to be closely identical with the mottling of human teeth.

In another group of experiments, chemical compounds were added to the food or water, using such as for one reason or another had been suspected of interfering with enamel calcification. When sodium flouride in concentrations of 0.025, 0.05, and 0.1 per cent was added to the diet, the incisors of rats began to lose their luster within a week, and in a month a corroded, pitted condition of the enamel could be observed. In 1925, McCollum had noted the abnormal color in the teeth of rats when amounts of fluoride only slightly above those occurring in natural foods had been added to the diet. Wells in the neighborhood of St David show a fluoride content of from four to seven parts per million. The well-water used by the family having the only children without the defect, that had been born and raised in the community, had a fluoride content of less than one part per million.

This work must be considered as advancing proof that mottled enamel is due to the fluoride content of the water supply of the afflicted communities. It adds another criterion to the list of those which must be taken into account in judging the suitability of a water supply. The 'brown stain' of mottled enamel is evidently a secondary condition and as yet has not been satisfactorily explained.

Abstracts

Early Lesions of Rheumatic Endocarditis.
By TIMOTHY LEARY, M D (Arch Path., 1932, xiii, 1-22)

The position of the author as medical examiner gave him opportunity to study the early phases of rheumatic endocarditis in persons who came to violent deaths while in apparent full health, or who died suddenly without hospitalization. Three patients, in the series utilized, provided the principal material. One was an apparently healthy boy of six years, whose death was due to violence, with an endocardial lesion of the mitral valve before verruca formation. An intermediate phase was found in a girl of 18 years, who had had mitral stenosis for eight years before her death, with an endocardial lesion of the tricuspid valve associated with verrucae formations in various stages. A late phase was obtained from a man, aged 51, who had an old, but not advanced, mitral process, with the lesion on the mitral valve, and showing pseudoverrucae due to thrombus formation. In the first case the contact edge of the valve was covered by a continuous layer of cells set on edge at right angles to the valve surface, giving the effect of an orderly palisade of cells guarding the injured valve surface. This must be interpreted as a reaction of defense against an injurious agent located on the surface. The cells of the palisade are believed to be evolved from fibroblasts. In the second case, the tricuspid valve showed a similar palisade arrangement between the verrucae and in the regions where no verrucae were found. In the third case pseudoverrucae made up of blood clot were found attached to areas of the mitral valve where there was a partially necrotic, dense and relatively acellular connective tissue. From this material it was possible to trace the evolution of the verrucae. Following injury to, and necrosis of, the cell palisade, the underlying fibro-

blastic tissue proliferates and groups of fibroblasts bulge upward at right angles to the surface underneath the hyaline necrotic masses. As the resulting verruca enlarges, histocytes appear among the fibroblasts [The phases of this process are well illustrated by 23 figures]

Streptococci Agglutination in Glomerulonephritis By B J CLAWSON, and MACNIDER WETHERBY (Proc Soc Exp Biol and Med, 1932, xxix, 566-567)

The streptococcic agglutinating titers of the serums of 20 patients with glomerulonephritis were determined for a strain of streptococci recovered from the blood of a patient having acute rheumatic fever. All serums agglutinated in dilutions as high as 1 800. Five agglutinated at 1 800, ten at 1 1600, one at 1 3200, three at 1 6400 and one at 1 12800. The agglutinating titers of these serums were considerably higher than those found with the same strain with the serums of 110 normal individuals, of 50 patients with acute rheumatic fever, and of 300 patients with chronic arthritis. The relative height of the streptococcic agglutinating titers in glomerulonephritis suggested (1) an etiologic relationship and (2) a possible biologic method for differentiating renal insufficiency due to glomerulonephritis from renal insufficiency associated with primary hypertension.

Bacteriological Investigations on the Blood, Synovial Fluid and Subcutaneous Nodules in Rheumatoid (Chronic Infectious) Arthritis By MARTIN H DAWSON, M D, MIRIAM OLIVESTAD, A M, and RALPH H BOOTS, M D (Arch Int Med, 1932, xlix, 173-180)

In this study the term 'rheumatoid arthritis' is used to designate that form of chronic multiple arthritis more commonly called 'chronic infectious' or 'atrophic ar-

thritis One hundred and five blood cultures, the majority in duplicate, were carried out on 80 patients suffering from rheumatoid arthritis, according to the technic of Cecil, Nicholls and Stainsby As control material, 31 samples of blood from normal persons and 16 samples of sterile agar were subjected to similar manipulations The blood cultures from patients suffering with rheumatoid arthritis failed to yield organisms that would be considered of etiologic significance No significant difference was observed between the bacteria found in the blood cultures of patients and those observed during the culture of the control material *Streptococcus viridans* was encountered occasionally during the culture of the control material as well as during the culture of specimens of the patients' blood Twenty-three specimens of synovial fluid from patients with rheumatoid arthritis yielded no organisms of etiologic significance Aerobic and anaerobic cultures of 12 subcutaneous nodules obtained from patients with rheumatoid arthritis likewise failed to yield organisms that could be considered of etiologic significance

Elliptical Human Erythrocytes By M C TERRY, M D, E W HOLLINGSWORTH, M D and VICENTE EUGENIO, B A (Arch Path., 1932, xiii, 193-206)

The authors have collected 50 instances of elliptical human erythrocytes, and have added two additional cases of their own The autopsy findings in one case are given Aside from a reddish purple color and semi fluid consistency in the bone marrow of the femur, no changes which could be associated with the anomaly of the erythrocytes were found When the blood of one of the patients was subjected to the action of hypotonic salt solution, the oval cells resembled normal erythrocytes in their behavior rather than the poikilocytes of a patient with anemia The oval shape of the cells was shown to depend upon structural and not upon local environmental factors The oval cells were found to be heavier than the round cells, and also more resistant than the round cells to the hemolytic action of hypotonic salt solution An analysis of the entire group of cases estab-

lishes the condition as a hereditary anomaly which is not incompatible with health, which may occur in whites, blacks and mulattoes, and which is about equally divided in incidence between the sexes It may be transmitted through either the male or female, and a generation may be skipped All four blood groups are represented among the reported cases

The Syndrome of Adrenal Hemorrhage in the New-Born By MAX A GOLDBLUM, M D, and MURRAY B GORDON, M D (Endocrinology, 1932, xvi, 165-181)

Thirty-seven cases of adrenal hemorrhage in the new-born and 38 in older infants, all offering some clinical information, were gathered from the literature To these, six personally observed instances, of which five were diagnosed during life, have been added From a study of these 81 cases it was concluded that an *intra vitam* diagnosis of adrenal hemorrhage in the new-born may be made on the basis of a definite syndrome This consists of two groups of symptoms: those due to acute adrenal insufficiency and those produced by internal hemorrhage Either one of these may predominate Acute insufficiency is made known by acute onset, high temperature, rapid respirations, petechial or purpuric rash, cyanosis and metabolic changes—especially hypoglycemia Associated with these are gastro-intestinal and nervous disturbances These may be accompanied or masked by signs of internal hemorrhage (shock collapse, weak pulse) and local signs of abdominal distress distention and the presence of masses in one or both kidney regions Suggested therapy consists of intravenous transfusion of blood, injection of glucose and the administration of a potent adrenal cortical extract

Iodine Poisoning and Iodism from Iodized Food By D A CANNIBALL, M D (Canadian Med Assoc J., 1932, xvi, 319-20)

Two cases are described in which a combination of iodism and iodine poisoning followed the use of iodized food The first patient had received 20 cc of iodine solution by the nasogastric method 8 x 1 cc per day for 10 days, and the second patient had received 10 cc of the same solution 4 x 1 cc per day for 10 days, in addition to the iodine in the food, for 10 days The first patient had received 20 cc of iodine solution 8 x 1 cc per day for 10 days, and the second patient had received 10 cc of the same solution 4 x 1 cc per day for 10 days, in addition to the iodine in the food, for 10 days

carial wheals over the knuckles, wrists, forearms, forehead, nose, lips, chin, cheeks, ears, and sides of the neck. These became bullous vesicles, many of which were hemorrhagic. Tough crusts formed, beneath which the epithelium regenerated, and recovery without scar formation was complete at the end of three months. A second patient gave substantially the same symptoms and signs following the supraglottic introduction of 30 c.c. of lipiodol to confirm a diagnosis of bronchiectasis. The author believes that this combination of the irritant poison effects of iodine with the skin eruptions of iodism in these cases must indicate rapid absorption from the gastro-intestinal tract and that this is made possible by swallowing the sputum. He suggests that patients should be instructed that at no time during the procedure, or afterwards as long as the taste or smell of oil is recognized, should the sputum be swallowed. Careful search during the fluoroscopic examination will reveal any lipiodol in the stomach and if sufficient to contain even one grain of iodine, it should be removed either by gastric lavage, induced vomiting, or a brisk

saline cathartic. Starch may be given as an antidote and continued as long as the vomited or aspirated material has a blue color.

A Pathologic Study of the Criteria Differentiating Chronic Gastric Ulcer, Cancer-on-Ulcer and Ulcerating Carcinoma of the Stomach. By W. H. BUEERMANN, (Northwest Medicine, 1932, xxxi, 49-54.)

From various sources the criteria to be applied in recognizing the development of gastric carcinoma upon gastric ulcer are assembled. In this manner the history of the evolution of this clinico-pathological conception is traced. The author finds that, at the present time, there is fairly general agreement that carcinoma does develop secondarily in a small percentage of chronic gastric ulcers. Definite pathologic criteria must be laid down and strictly adhered to in differentiating cancer-on-ulcer from ulcerating carcinoma. Clinically, the danger lies not so much in the possibility that cancer will develop upon a given gastric ulcer, as that an early ulcerating carcinoma may be masquerading as a benign calloused ulcer.

Reviews

It is with pleasure that attention is called to the fact that all of the books selected for review this month deal with the History of Medicine. This is a good sign. It is another indication of the growing interest in the cultural side of our work. It is in line with the increasing recognition given the subject of Medical History on the program of the San Francisco Meeting of the College, with the successful continuation in this country of such a journal as the *Annals of Medical History*, and with the increasing strength of both local and national societies for the prosecution of the study of this subject.

This is a period of notable anniversaries in Medical History. Less than two years ago was celebrated the tercentenary of the introduction of cinchona into medicine of the civilized world. This year, on October 24, another tercentennial should be noted, the birth of Antony van Leeuwenhoek. On March 24, the medical world did honor to the memory of Robert Koch, for fifty years before that day he announced the discovery of the tubercle bacillus.

It is well that so many local histories of medicine are being written. There should be one for every state and province. Material should be re-

corded while we still have with us those who saw the beginnings of so much that has proved of historical import in the growth of medical teaching and practice in North America

History of Medicine in the United States
By FRANCIS R. PACKARD, M.D., Editor,
Annals of Medical History 103 illustrations
Volume I, xxv + 656 pages, volume II, 666 pages Paul B. Hoeber, Inc.,
New York City, 1931 Price, \$12.00, for
two volumes

The production of a History of Medicine in the United States by the distinguished editor of the *Annals of Medical History* is an event of prime importance. To the more than 1300 pages of this great work the author has brought the experience and method of a trained historian who skillfully combines original source material with the exposition necessary to develop his theme. He is at his best in those sections to which this method is applicable. Since this was true of the greater part of the text, that statement alone constitutes enthusiastic praise. He succeeds admirably in writing interestingly and at the same time incorporating names and dates and facts. Only in those portions which deal with more recent events of somewhat local significance, in particular, the history of the individual medical schools, does interest lag and the method become encyclopedic. It should be obvious that in these topics are to be treated at all they must be thus sketchily covered. If the method of the historian seeking a full presentation from original sources had been applied to this portion, each short section would have become a monograph and no one human being could have accomplished the task. The author fully appreciated the limitations imposed for he states in the preface that if he had waited to gather complete data to a period even as remote as 1850, the task would not have been completed. The format and typography are excellent, the illustrations well chosen and well produced. A double index is provided one of personal names and one of subjects, also a bibliography of twenty-four pages. This work should be in the possession of all

interested in the History of Medicine. Seventy-five per cent of it can be read with interest by any practitioner and all of it is of great value for purpose of reference.

Introtop to Harvey Backgrounds of Medical History By C. N. B. CHASE, M.D.,
Assistant Professor of Clinical Medicine,
College of Physicians and Surgeons, Col-
umbia University, New York. Foreword
by HENRY FAIRFIELD OSBORN, Sc.D.,
LL.D. xxv + 324 pages, 4 illustrations,
five tables Paul B. Hoeber, Inc., New
York City, 1931, Price \$3.75

The author's seminars for fourth year medical students of The College of Physicians and Surgeons of New York are reflected in the pages of this book. In a series of chapters, each of which might serve as the basis for an informal exercise in Medical History, the background of the subject is developed. Preceding each the subject matter is briefly outlined, and in the last 20 pages, book lists are given, arranged to illustrate and complement the material of each chapter. Thus this book lends itself particularly to the library method of presentation. Illustrative material is found in a group of historical records and quotations from, or about, Servetus, Harvey, Copernicus, Galileo, Descartes, and Spinoza. We agree with the distinguished author of the foreword, that "The present volume will serve as an introduction to longer works, bringing the History of Medicine within the reach of medical undergraduates and those novices and initiates with whom the art of healing may become a delightful vocation if not a vocation. To this large and rapidly increasing class of professional and nonprofessional readers we heartily recommend 'Introtop to Harvey Backgrounds of Medical History'."

History of Medicine in the Province of Quebec By MARIE I. ANAST, B.A.,
M.D., 97 pages, 10 illustrations & 144 illustrations McGill University, Montreal
Canada 1931 Price, \$5.00

This outline of the History of Medicine in the Province of Quebec was written for the publication of the *Annals of Medical History*. It is a valuable contribution to the history of medicine in the Province of Quebec.

covering the period from the discovery of Canada to 1800, the late Dr Georges Ahern assumed responsibility. The second part, 1800 to the present time, was particularly assigned to Dr Abbott. Through the death of Dr Ahern it became necessary for Dr Abbott to assume the responsibility of bringing this material together in a unified form. Dr Abbott has succeeded in presenting a very interesting and informative account of the medical history of the province. While concerned with tracing the larger movements and the growth of significant institutions, Dr Abbott has made free use of original sources with quotations, personal anecdotes, official records, and other citations which add greatly to the interest. The sections on Primitive Medicine, Scurvy among the First Settlers, the Rise of the Early French Hospitals, Michel Sarrazin, Inoculation and Vaccination, Great Epidemics of the Nineteenth Century, and Dr James Barry are all of much more than local interest. Dr Abbott has made a worthwhile contribution, not only to the Medical History of the Province of Quebec, but to that of the New World.

A Doctor of the 1870's and 80's By WILLIAM ALLEN PUSEY, sometime President of the American Medical Association and of the American Dermatological Association. xiii + 153 pages. Illustrated. Charles C Thomas, Springfield, Illinois. Price, \$3.00 postpaid.

As a boy, the reviewer read and reread a simply written book entitled "The Country Doctor". Its authorship has long ago passed from memory, but its faithful reflection of the life and activities of a general practitioner in the prairie country rang true, and the skillful blending of comedy and pathos made an indelible impression. In Pusey's book we find again the record of the life and activities of the general practitioner in a rural community. This alone would justify its writing, but here the picture is drawn with skill and with tenderness. Between the lines one senses the anxiety of the son who fears that he will write too much of the virtues of his hero-father, and at the same time fears he is writing too little to measure up to what he knows to

have been the just estimate of the man. This book should live on. It is not only a contribution to Medical History in the United States, but it is also a human document good to be read by the medical sons of medical fathers for more than one generation.

California Medicine (A Review) By JOHN WILLIAM SHUMAN, M.D., F.A.C.P. 182 pages. A. R. Elliott Publishing Company, 53 Park Place, New York City. Privately printed.

As previously stated it should be a source of great satisfaction to all interested in the history of Medicine in the United States that so many local histories have appeared in the last few years. This timely effort on the part of Dr Shuman has made possible the preservation of the evidence of eye witnesses to many highly significant developments. In but a few years more such accounts will have become impossible. In *California Medicine*, the author records much that is of value, particularly to those whose special interest is in Los Angeles and its environs. To others medical, it will prove entertaining and informative, especially in regard to Indian and early Spanish Medicine and the doctors of the Gold Rush days. The author is to be congratulated on his easy narrative style. It is to be regretted that but a very limited edition is available.

Builders of American Medicine Being a Collection of Original Papers Read before the Victor C. Vaughan Society of the University of Michigan Medical School viii + 243 pages, 9 illustrations. George Wahr, Publisher, Ann Arbor, Michigan, 1932. Price, \$2.00.

At the University of Michigan a self-perpetuating group of senior medical students is organized as The Victor C. Vaughan Society for the study of Medical History. The present volume contains twelve essays read before this group during the year 1930-31. The "Builders" who are the subjects of these essays are Zabdiel Boylston, Benjamin Rush, Ephraim McDowell, William Beaumont, Samuel D. Gross, Sr., Oliver Wendell Holmes, Austin

Flint, William Pepper, Silas Weir Mitchell, John Shaw Billings, Walter Reed and Victor C Vaughan. Naturally, a senior medical student can seldom be a researcher in Medical History in the sense of bringing forth new knowledge from hitherto unknown or unappreciated original sources. Yet the vigor and freshness of the enthusiastic amateur stand out in these chapters, which must, of necessity, be largely fusions of tales that have been told before. This attractive little book deserves a wider distribution than that which it is likely to receive.

The History of Medicine A Short Synopsis By BERNARD DAWSON, M.D. (Lond.), F.R.C.S. (Eng.) xiv + 160 pages, 31

illustrations. The Macmillan Company, New York City, 1932. Price \$2.50.

This small book contains a series of lectures delivered to junior medical students of Adelaide University. These lectures are intended to portray the continuity and increasing volume of the stream of medical knowledge rather than to present the details of the History of Medicine. The material is presented under seven chapter heads: Primitive Medicine, The Grecian Period, The Greco-Roman Period, the Dark Ages and the Hippocratic Tradition, The Middle Ages and the Universities, The Renaissance, and The Period of Consolidation. The style of this book is pleasing and the typography excellent. It can be recommended as fulfilling its stated purpose.

College News Notes

Acknowledgement is made of the receipt of gifts to the College Library of Publications by members, as follows:

Dr Frank J Altschul (Associate), Long Branch, N.J.—2 reprints,

Dr Miles J Breuer (Fellow), Lincoln, Nebr.—1 reprint,

Dr Grafton T Brown (Fellow), Washington, D.C.—1 reprint,

Lt Col Alexander T Cooper (Fellow), Fort Myer, Va.—1 reprint,

Dr Edward E Cornwall (Fellow), Brooklyn, N.Y.—1 reprint,

Dr John J Dumphy (Associate), Worcester, Mass.—2 reprints,

Dr Hyman I Goldstein (Associate), Camden, N.J.—3 reprints,

Dr John R. Hamel (Fellow), Portland, Maine—2 reprints,

Dr Ronald L Hamilton (Fellow), Sayre, Pa.—1 reprint,

Dr Robert A Knox (Fellow), Washington, Pa.—1 reprint,

Dr George B Lake (Associate), Highland Park, Ill.—3 reprints,

Dr David E. Markson (Fellow), Chicago, Ill.—1 reprint,

Dr Oliver T Osborne (Fellow), New Haven, Conn.—1 reprint,

Dr Virgil G Presson (Associate), Tucson, Ariz.—1 reprint,

Dr Karl Rothschild (Associate), New Brunswick, N.J.—2 reprints,

Dr Virgil E Simpson (Fellow), Louisville, Ky.—3 reprints,

Dr Carl V Vischer (Fellow), Philadelphia, Pa.—1 reprint.

Dr Guy G Iunsford (Fellow), Commissioner of Health, Milton, Georgia, addressed the annual meeting of the Georgia Public Health Association, January 22, 1932, on "Typhoid and Sanitation."

Dr Arthur C Morgan (Fellow), Philadelphia, Pa., was recently appointed by Governor Pinchot of Pennsylvania as a member of the State Board of Medical Education and Licensure.

Capt Kent C Mellorn, M.C., U.S.N. (Fellow), Washington, D.C., was elected lately from the Bureau of Medicine and Surgery, Navy Department, to the State Department by the Senate to the American Delegation to the General Assembly of the League of Nations.

the Medical Corps of the Navy in 1907. Since September, 1930, Captain Melhorn has been in charge of the Division of Personnel, Bureau of Medicine and Surgery.

Dr. Hyman I Goldstein (Associate), Camden, N. J., is the author of an article in the *Medical Times* (N.Y.) for January, 1932, entitled "Mitral Stenosis." He is also the author of an article in the *Journal of the Medical Society of New Jersey* for February, 1932, entitled "Erythema Nodosum and Erythema Multiforme," and of one in *International Clinics* (Phila.) for March, 1932, entitled "Recent Advances in Treatment."

Dr. E. J. G. Beardsley (Fellow), Philadelphia, Pa., Governor for Eastern Pennsylvania, was the guest speaker at the Cambria County Medical Society at Johnstown, Pa., on February 11, 1932. His subject was "The Science and the Art of Medicine."

Dr. David E. Markson (Fellow), Chicago, Ill., read a paper entitled "Newer Concepts on Etiology and Treatment of Arthritis" before the DuPage County Medical Society on January 16, 1932. On January 28, he presented the "Report of a Case of Diabetic Coma, with Blood Sugar of 900 mg., with Recovery" before the staff of the Norwegian American Hospital, and on March 3, addressed the North Side Branch of the Chicago Medical Society on "Therapeutic Fever in the Treatment of Arthritis."

Dr. John L. Garvey (Fellow), Milwaukee, Wis., recently presented a paper on "Calcified Angiomas of the Brain," together with a report of a case, before a meeting of the Chicago Neurological Society.

At a Symposium on Arthritis given by the Section of Internal Medicine of the Los Angeles County Medical Association on February 3, 1932, the following Fellows of the College contributed to the program:

"Arthritis Due to a Definite Organism"

Dr. Roland S. Cummings, Los Angeles
Discussion opened by Dr. Roy Thomas,
Los Angeles

"Arthritis Due to Metabolic Disturbances"
Dr. S. M. Alter, Los Angeles,
Discussion opened by Dr. Paul B. Roen,
Hollywood

"Arthritis Deformans"

Dr. John V. Barrow, Los Angeles
Dr. John W. Shuman, Los Angeles, is President of the organization and Dr. John V. Barrow, Los Angeles, is Secretary. Dr. S. M. Alter was Chairman for the Symposium.

Dr. Edward J. Engberg (Fellow), St. Paul, Minn., read a paper on "The Present Extent and Value of Annual Registration" before the Federation of State Medical Boards of the United States held in Chicago on February 15 and 16, 1932, in connection with the Annual Congress on Medical Education, Medical Licensure, and Hospitals.

Dr. Paul J. Connor (Fellow), Denver, Colo., was elected President of Staff of the Presbyterian Hospital of Colorado at a meeting of the Staff in January.

Dr. Erwin D. Funk (Fellow), Wyomissing, Pa., is in Germany pursuing further studies in Pathology.

An interesting Annual Report of the St. Edwards Mercy Hospital of Ft. Smith, Ark., was recently received. Dr. S. J. Wolferman (Fellow) is Chief of Staff. Dr. Arless A. Blair (Fellow) is Vice President of the Clinical Staff as well as being a member of the Executive Staff.

Dr. Edward V. Goltz (Fellow), St. Paul, Minn., was elected President of the Ramsey County Medical Society at the November meeting.

Dr. Lorenz W. Frank (Fellow), Denver, Colo., was elected President of the Medical Society of the City and County of Denver at the annual meeting on January 4, 1932.

Dr. Edward W. Jackson (Fellow), formerly of Rochester, N. Y., has recently become associated with the Ponton-Brown

Clinic Hospital of Edinburg, Texas, as Chief of the Medical Staff

Dr William Engelbach (Fellow), New York City, addressed the American-Hungarian Medical Association at the New York Academy of Medicine on February 15, 1932, his subject being "The Growth Hormone" Dr Englebach also delivered an address on "The Anterior Pituitary Lobe" before the Bedford Medical Society, February 25, 1932

Upon examination of the March 1 issue of *Progress Notes* published by the Atlantic City Hospital, Atlantic City, N J, we note that the following Fellows and Associates of the College are on the General Staff for 1932 Dr Samuel Barbash (Fellow), Dr D Ward Scanlan (Fellow), Dr Samuel I. Salasin (Fellow), Dr Clarence L. Andrews (Fellow), Dr Sidney Rosenblatt (Associate), Dr Harold S. Davidson (Fellow), Dr Philip Marvel, Jr (Fellow), and Dr Hilton S. Read (Associate) Dr Philip Marvel, Sr, (Fellow) and Dr W. Blair Stewart (Fellow), Governor for New Jersey, are Honorary Members of the Staff

Dr Frederic J. Farnell (Fellow), Providence, R I, Chairman of the Public Welfare Commission, State of Rhode Island, is the author of a signed article appearing in *The United States Daily*, Washington, DC, February 17, 1932, entitled "Plan for Public Welfare Work in Rhode Island"

The following Fellows of the College are members of the Committee on Nominations of the National Tuberculosis Association: Dr Stuart Pritchard, Battle Creek, Mich., Chairman, Dr Frederick T. Lord, Boston, Mass., Dr Munford Smith, Los Angeles, Calif. At the Twenty-eighth Annual Meeting of the National Tuberculosis Association, to be held at the Antlers Hotel, Colorado Springs, Colorado, June 6-9, 1932, Dr Pritchard will give the Report of the Committee on Nominations.

At this meeting, according to the Preliminary Program, the following Fellows will present papers: Dr Gertrud B. Welch,

Colorado Springs, Dr Clarence L. Hyde, Akron, Ohio, Dr John W. Flinn, Prescott, Ariz., Dr E. K. Geer, St. Paul, Minn., Dr H. A. Burns, Ah-gwah-ching, Minn., and Dr Carl H. Greene, Rochester, Minn.

Dr I. D. Bronfin (Fellow), Denver, Colo., will speak at the Spring Meeting of the American Sanatorium Association, June 6 and 7, 1932, to be held at the Brown Palace Hotel, Denver, Colo., and F. E. Harrington (Fellow), Minneapolis, Minn., and Dr Benjamin W. Black (Fellow), Oakland, Calif., will appear on the program of the American Public Health Association, whose Western Branch Meeting will be held June 9-11, 1932, in Denver.

Dr Ada E. Schweitzer (Fellow), Indianapolis, Indiana, Child Hygiene Director for the Indiana State Board of Health, Division of Infant and Child Hygiene, is responsible, in conjunction with Dr Wm. F. King, State Board of Health Commissioner for Indiana, for the novel idea of designating May Day as Child Health Day in that State. Pamphlets have been broadcast to homes, churches, and institutions of various kinds throughout the state, suggesting programs of activity and instruction along health lines for use in observing this special health day. Individuals and groups putting these or other plans into practice are urged to report the same to Dr Schweitzer in order that the movement may incorporate permanently the advances made this year.

Dr V. C. Rowland (Fellow), Cleveland, Ohio, was the guest of Dr A. B. Brower (Fellow), Dayton, Ohio, Governor of Ohio, at a dinner at the Van Cleve Hotel on March 4, 1932. Later the same evening he addressed the Montgomery County Medical Society on "Differential Diagnosis of Chronic Colitis." In route to Dayton, Dr Rowland had spoken before the Fayette County Medical Society at Watertown, Ohio, in connection with the celebration of Diphtheria Immunization, subject being "Periodic Health Examinations." At this meeting he repeated the Periodic Health Examination of the Fayette County Medical Association.

Dr Alfred Friedlander (Fellow), Cincinnati, Ohio, delivered an address before the Medical Forum of Pittsburgh on the evening of February 13, embodying the results of studies on the "Reticulocyte Count in Normal and Abnormal Conditions"

Dr Albert W Ferris (Fellow), East Orange, N J, has resigned his position as Senior Physician on the Staff of the Glen Springs Health Resort, Watkins Glen, N Y, because of illness. Dr Ferris spent nearly fifteen years in this service, besides having been formerly President of the N Y State Commission in Lunacy (now the Department of Mental Hygiene), Medical Editor for many years of the *New International Encyclopedia and Year Book*, and the author of over forty articles on medical topics, in various medical publications. He has now retired from practice and is living at 111 N Walnut Street, East Orange, N J

Dr Walter M Simpson (Fellow), Dayton, Ohio, was a guest of the Medical Service of the Ffth Avenue Hospital, New York City, on February 19, 1932, presenting a paper on "Tularemia" on that evening

Dr Charles J Bloom (Fellow), New

Orleans, held a clinic on March 3 in the city of McComb, Mississippi, and the same evening gave a paper entitled "Common Respiratory Infections in Infants and Children"

Dr Joseph H Barach (Fellow), Pittsburgh, addressed The Mohoning County Medical Society at Youngstown, Ohio, on February 16, 1932. Dr Barach spoke on the topic, "The Etiology, Classification, and Treatment of High Arterial Pressure"

Dr Anthony Bassler (Fellow), New York City, lectured to the senior students of Jefferson Medical College and to the senior and junior students of Hahnemann Medical College of Philadelphia on March 23, 1932, speaking on the Physiology of the Pancreas, with special regard to his test for judging the efficiency of the external secretion of the pancreas and its clinical application

On February 24, 1932, Dr J Reid Broderick (Fellow), Savannah, Georgia, addressed the First District Meeting of the Georgia Medical Society in Statesboro, Georgia, on the subject, "Bronchial Asthma"

OBITUARIES

DOCTOR HUGH SPAULDING WILLSON

Doctor Hugh Spaulding Willson (Fellow), died from acute coronary thrombosis at his home in La Jolla, California, on the 12th of December

Dr Willson was born in 1877 at Plain View, Minnesota. He was graduated in medicine by the University of Minnesota in 1904. After practicing as assistant city physician in Minneapolis for eighteen months he went to Crystal, North Dakota, where he practiced until 1912. Following a year's service with the Mayo Clinic at Rochester, Minnesota, Doctor Willson went to Minneapolis

where he built up a gastro-intestinal clinic in which he, and the physicians he had associated with him, conducted a large and widely known practice. At the outbreak of the war, Doctor Willson went into Military service as a consulting physician. After nine months at Camp Kearney he went overseas with Base Hospital No 70. After the war Doctor Willson reopened the Clinic in Minneapolis. He remained there until 1926, when, forced by ill-health, he went to La Jolla, California, where his wife, Mary Richmond, to whom he was married in 1907, now survives him. Doctor Willson found the rest and change to

California so beneficial that he opened offices in La Jolla. The return to activities in his profession gave him much comfort and brought him high esteem among his many friends and patients who deeply regret his untimely death.

(Furnished by EGERION CRISPIN, M.D., F.A.C.P., Governor for Southern California)

DOCTOR HOWARD H. BELL

Dr. Howard H. Bell (Fellow), St. Louis, Missouri, died January 7, 1932, age forty-seven years.

Dr. Bell was born at Lewistown, Pennsylvania, attended High School there, and later entered the Philadelphia College of Pharmacy, from which he graduated as a Pharmaceutical Chemist in 1907. In 1909 he was awarded the degree of Doctor of Pharmacy from the same institution. He entered the University of Pennsylvania School of Medicine, and graduated with the degree of Doctor of Medicine in 1912. He was Instructor in Pathology and Bacteriology at the University of Alabama, 1913 to 1919, Assistant Instructor and Associate in the Department of Pathology, and later Associate Professor of Bacteriology at the Washington University School of Medicine, St. Louis, these appointments extending from 1914 to 1924. During 1924 and the first half of 1925, he was connected with the Department of Medicine of the University of Cincinnati, and in 1925 went to the St. Louis University School of Medicine as Assistant in Medicine, which appointment he held at the time of his death. He was also Tuberculosis Controller for the city of St. Louis.

Dr. Bell was the author of many publications appearing in the leading journals of the country. During the World War he served at Rouen, Dijon, Langres, and in the Balkans. In all he served twenty-eight months in foreign service successively as First Lieutenant, Captain and Major. He was cited by the Officers Municipaux de Langres and was decorated by the King of Rumania.

He was a member of the St. Louis Medical Society, an Ex-President of the Trudeau Club, a member of the Missouri State Medical Society, a Fellow of the American Medical Association, as well as being a member of many other scientific organizations. He was elected a Fellow of the American College of Physicians on April 8, 1929.

DOCTOR MALLIE ADKIN CLARK

Dr. Mallie Adkin Clark (Fellow), Macon, Georgia, died February 6, 1932.

Dr. Clark was born in Russell County, Alabama, September 1, 1860. His preliminary education was obtained under his father's direction, and in 1885, he received his A.B. degree from Mercer University, and in 1911, his I.L.D. degree from the same institution. He received his M.D. degree from Bellevue Hospital Medical College in 1890. For several years thereafter, he practiced medicine in Bluffton and Barnesville, Georgia, coming to Macon in 1897, where he remained in active practice until the time of his death. From 1898 he was on the Faculty of Mercer University as teacher of Medical Jurisprudence in the Law School and Maternal Medicine in the School of Pharmacy.

Dr Alfred Friedlander (Fellow), Cincinnati, Ohio, delivered an address before the Medical Forum of Pittsburgh on the evening of February 13, embodying the results of studies on the "Reticulocyte Count in Normal and Abnormal Conditions"

Dr Albert W Ferris (Fellow), East Orange, N J, has resigned his position as Senior Physician on the Staff of the Glen Springs Health Resort, Watkins Glen, N Y, because of illness. Dr Ferris spent nearly fifteen years in this service, besides having been formerly President of the N Y State Commission in Lunacy (now the Department of Mental Hygiene), Medical Editor for many years of the *New International Encyclopedia and Year Book*, and the author of over forty articles on medical topics, in various medical publications. He has now retired from practice and is living at 111 N Walnut Street, East Orange, N J

Dr Walter M Simpson (Fellow), Dayton, Ohio, was a guest of the Medical Service of the Fifth Avenue Hospital, New York City, on February 19, 1932, presenting a paper on "Tularemia" on that evening

Dr Charles J Bloom (Fellow), New

Orleans, held a clinic on March 3 in the city of McComb, Mississippi, and the same evening gave a paper entitled "Common Respiratory Infections in Infants and Children"

Dr Joseph H Barach (Fellow), Pittsburgh, addressed The Mohoning County Medical Society at Youngstown, Ohio, on February 16, 1932. Dr Barach spoke on the topic, "The Etiology, Classification, and Treatment of High Arterial Pressure"

Dr Anthony Bassler (Fellow), New York City, lectured to the senior students of Jefferson Medical College and to the senior and junior students of Hahnemann Medical College of Philadelphia on March 23, 1932, speaking on the Physiology of the Pancreas, with special regard to his test for judging the efficiency of the external secretion of the pancreas and its clinical application

On February 24, 1932, Dr J Reid Broderick (Fellow), Savannah, Georgia, addressed the First District Meeting of the Georgia Medical Society in Statesboro, Georgia, on the subject, "Bronchial Asthma"

OBITUARIES

DOCTOR HUGH SPAULDING WILLSON

Doctor Hugh Spaulding Willson (Fellow), died from acute coronary thrombosis at his home in La Jolla, California, on the 12th of December

Dr Willson was born in 1877 at Plain View, Minnesota. He was graduated in medicine by the University of Minnesota in 1904. After practicing as assistant city physician in Minneapolis for eighteen months he went to Crystal, North Dakota, where he practiced until 1912. Following a year's service with the Mayo Clinic at Rochester, Minnesota, Doctor Willson went to Minneapolis

where he built up a gastro-intestinal clinic in which he, and the physicians he had associated with him, conducted a large and widely known practice. At the outbreak of the war, Doctor Willson went into Military service as a consulting physician. After nine months at Camp Kearney he went overseas with Base Hospital No 70. After the war Doctor Willson reopened the Clinic in Minneapolis. He remained there until 1926, when, forced by ill-health, he went to La Jolla, California, where his wife, Mary Richmond, to whom he was married in 1907, now survives him. Doctor Willson found the rest and change to

California so beneficial that he opened offices in La Jolla. The return to activities in his profession gave him much comfort and brought him high esteem among his many friends and patients who deeply regret his untimely death.

(Furnished by EGERION CRISPIN, M.D., F.A.C.P., Governor for Southern California)

DOCTOR HOWARD H. BELL

Dr. Howard H. Bell (Fellow), St. Louis, Missouri, died January 7, 1932, age forty-seven years.

Dr. Bell was born at Lewistown, Pennsylvania, attended High School there, and later entered the Philadelphia College of Pharmacy, from which he graduated as a Pharmaceutical Chemist in 1907. In 1909 he was awarded the degree of Doctor of Pharmacy from the same institution. He entered the University of Pennsylvania School of Medicine, and graduated with the degree of Doctor of Medicine in 1912. He was Instructor in Pathology and Bacteriology at the University of Alabama, 1913 to 1919, Assistant Instructor and Associate in the Department of Pathology, and later Associate Professor of Bacteriology at the Washington University School of Medicine, St. Louis, these appointments extending from 1914 to 1924. During 1924 and the first half of 1925, he was connected with the Department of Medicine of the University of Cincinnati, and in 1925 went to the St. Louis University School of Medicine as Assistant in Medicine, which appointment he held at the time of his death. He was also Tuberculosis Controller for the city of St. Louis.

Dr. Bell was the author of many publications appearing in the leading journals of the country. During the World War he served at Rouen, Dijon, Langres, and in the Balkans. In all he served twenty-eight months in foreign service successively as First Lieutenant, Captain and Major. He was cited by the Officers Municipaux de Langres and was decorated by the King of Rumania.

He was a member of the St. Louis Medical Society, an Ex-President of the Trudeau Club, a member of the Missouri State Medical Society, a Fellow of the American Medical Association, as well as being a member of many other scientific organizations. He was elected a Fellow of the American College of Physicians on April 8, 1929.

DOCTOR MALLIE ADKIN CLARK

Dr. Mallie Adkin Clark (Fellow), Macon, Georgia, died February 6, 1932.

Dr. Clark was born in Russell County, Alabama, September 1, 1866. His preliminary education was obtained under his father's direction, and in 1885, he received his A.B. degree from Mercer University, and in 1911, his LL.D. degree from the same institution. He received his M.D. degree from Bellevue Hospital Medical College in 1890. For several years thereafter, he practiced medicine in Bluffton and Barnesville, Georgia, going to Macon in 1897, where he remained in active practice until the time of his death. From 1898, he was on the Faculty of Mercer University as teacher of Medical Jurisprudence in the Law School, and *Materia Medica* in the School of Pharmacy. For sev-

eral years, he was a member of the Board of Trustees of this university

Dr Clark had been an active member of the local medical society in Macon for many years, and was past President of the Medical Association of Georgia, and at the time of his death was its Parliamentarian. He was a Fellow of the American Medical Association, and was elected a Fellow of the American College of Physicians on January 1, 1921

Dr. Clark was a member of the staff of the Macon Hospital for many years, and had been a member and chairman of the Governing Board of that hospital

He was pre-eminently a student,

setting aside a part of every day for real study. His knowledge of medical sciences was well nigh encyclopedic. Those who sought of him information often said he seemed not to forget anything he had read. He gave willingly of his time and talents to those who sought his assistance, his opinion was respected. With him, his profession was his life; his recreation consisted of study of science and literature. He was devoted to his patients and felt keenly their sorrows and rejoiced in their joys

(Furnished by JAMES A FOUNTAIN, M D, F A C P, President, Medical Society of Bibb County)

The Importance of Finger-Borne Infection

"IN THE transfer of this type of infection [diphtheria] from one person to another, the fingers are probably the chief agents. It has been said, 'Who can doubt that if the salivary glands secreted indigo, the fingers would continuously be stained a deep blue, and who can doubt that if the nasal and mouth secretions contain the germs of disease these germs will be almost as constantly found upon the fingers?' All successful commerce is reciprocal and in this universal trade of human saliva the fingers not only bring foreign secretions to the mouth of their owner, but there, exchanging them for his own, distribute the latter to everything that the hand touches. This happens not once, but scores and hundreds of times during the day's round of the individual. Everyone is busily engaged in this distribution of saliva, so that the end of each day finds this secretion freely distributed on the doors, window sills, furniture, and playthings in the home, the straps of trolley cars, the rails and counters and desks of shops and public buildings, and, indeed, upon everything that the hands of man touch. What avails it if the germs do die quickly? A fresh supply is furnished each day'

"Bearing in mind the aforementioned fundamental principles, the following

measures are recommended for the prevention of diphtheria, in the application of which every parent, schoolteacher, and family physician should render active cooperation (1) Strict adherence to the rules of personal hygiene, and (2) the immunization of all people who are likely to have diphtheria as shown by the Schick test"

(From *Health News*, United States Public Health Service, March 16, 1932)

SCIENTIFIC ARTICLES IN FORTHCOMING NUMBERS OF THE ANNALS OF INTERNAL MEDICINE

The May Number

- | | | |
|--|--|--------------------------------------|
| Rheumatic Heart Disease | A Review | CLOUGH TURRILL BURNETT |
| Early Manifestations of Rheumatic Infections in Young Children | | C C McLEAN |
| Causes, Classification and Differential Diagnosis of Anemias | Based on the Detailed Examination of over 200 Patients and a Study of the Literature | EDWIN E OSGOOD AND HOWARD D HASKINS |
| A Comparative Study of the Use of Whole Liver, Liver Extract and Vitellin | | HUGO A FREUND AND ALVIN E PRICE |
| Raynaud's Disease Affecting Men | | EDGAR V ALLEN AND GEORGE E BROWN |
| Does Liver Therapy Benefit the Diabetic? | | ELMER L SEVRINGHAUS |
| Primary Sclerosis of the Pulmonary Artery | Report of a Case | EDGAR R PUND AND THOMAS B PHINIZY |
| Gonorrheal Endocarditis | Summary of the Literature and Report of a Case | ARTHUR M HOFFMAN AND FLOYD C TAGGART |
| The Significance of Lymphatic Tissue and Adenoma-like Areas in the Thyroid Gland | | L R HIMMELBERGER |
| Pulmonary Lesions in Human Tularemia | Pathologic Review and Report of a Fatal Case | STAIGE D BLACKFORD |
| Oliver Goldsmith, M D | | LOUIS H RODDIS |

The June Number

- An Experimental Basis for Intravenous Vaccine Therapy in Chronic Arthritis
with a Summary of Results Obtained in Patients B J CLAWSON AND M. WETHERBY
- Hypertension and Diabetes HENRY J JOHN
- The Fallacy of the Weighed Diet in the Treatment of Diabetes Mellitus
. HELMUTH ULRICH
- Myxedema A Case Report HENRY B GOTTEN
- Hypothyroidism without Myxedema JOHN B YOUMANS AND SAMUEL S RIVEN
- Ventricular Paroxysmal Tachycardia, with Report of a Case
. EDWARD W. HOLLINGSWORTH
- Control of the Tick Borne Diseases, Methods and Economics . NOXON TOOMEY
- The Local and Constitutional Pathology of Bronchial Asthma IAN C MACDONALD
- The Etiology of Colds JOHN E WALKER
- A Layman Considers Migraine WALTER B SHEPPARD

Rheumatic Heart Disease

A REVIEW*

By CLOUGH TURRILL BURNETT, M D , F A C P , *Denver, Colorado*

THE large volume of literature which has appeared in recent years relating to various phases of rheumatic fever and rheumatic heart disease seemed to require some correlation. An attempt at this resulted in the following review.

While the earliest description of rheumatic fever appeared prior to the middle of the seventeenth century, and the best of these in 1676 by Sydenham, it was not until more than a century later, in 1788, that a clear description of rheumatic heart disease was published by David Pitcairn of St Bartholomew's in London. Prior to this, Storck and others had noted changes in the thoracic viscera in cases of rheumatism coming to autopsy.

Dillon,⁶² in 1850, and Gramshaw,⁶³ in 1853, used the term 'Rheumatic Carditis' in the titles of published articles. Stokes,¹ in 1853, frequently used this term. He observed that "disturbance of the heart's action, even though without any physical sign of inflammation, when arising in the course of rheumatic fever, is to be considered as showing the proclivity to, if not the existence of, carditis" (page 523), and that "rheumatic fever does not necessarily coexist with arthritis" (page

46). He also made the valuable observation—ofttimes forgotten in these later days—that the cardiac involvement may precede that of the joints (page 47).

INCIDENCE

A recent editorial appearing in *Colorado Medicine* raises the question of the value of conclusions drawn from mortality statistics in heart disease. While the inaccuracy of individual death certificates is evident, this basis of study remains at the present day the principal source of information as to the incidence and hence of the importance of any group of diseases. Therefore at the outset, reference must be made to mortality and, so far as obtainable, to morbidity statistics. During the past fifty years the deaths from tuberculosis declined 44 per cent, while the deaths from heart disease increased 42 per cent, and during the past twenty-five years in the United States Registration Area the deaths from heart disease outnumber those from tuberculosis. At the present time heart disease ranks as the leading cause of death. The local importance of heart disease is stressed by Washburn² who wrote, "In Denver, deaths from tuberculosis fell from nearly 700 in 1917 to 459 in 1927 while heart deaths increased from 157

*From the University of Colorado School of Medicine

in 1917 to 449 in 1927." The same author stated, "If we attempt to classify the deaths at all ages according to etiology we can estimate that approximately 30 to 35 per cent of the whole number are due to rheumatic heart disease."

Heart disease may be divided into three age groups and these in general represent etiological groups. Up to the age of forty the great majority of cases of heart disease are rheumatic in origin. Twenty-five per cent of all cardiac deaths fall in this period.³ Of five hundred children observed by Wilson⁴ and her associates in a heart clinic, 12 per cent died and 88 per cent of the deaths were due to rheumatic heart disease. In New York City⁵ heart disease was found to be the leading cause of death among school girls. Among school boys it ranks second only to accidental death. The same records show that heart disease stands second as cause of death in young adults ranging in age from fifteen to nineteen years.

The second age period in heart disease is from forty to sixty years, when syphilis is the most important cause of death. The third period extends from sixty years on, when cardiac deaths are chiefly due to degenerative changes.

It is unfortunate that we have no satisfactory morbidity statistics, since heart disease and rheumatic fever are not reportable diseases, but Emerson³ estimated that for every death from heart disease there are probably seventeen people suffering from heart disease, while there are only seven cases of tuberculosis for every death. Dublin³ was more conservative, estimating ten cases for every death from heart

disease, and stating that at ten years of age an individual is three times as likely to die from heart disease as from tuberculosis.

Deductions drawn from the incidence of rheumatic fever are of doubtful value since the conception of what constitutes rheumatic fever is and has been rapidly changing in the past decade. Practically all figures obtainable relate to frank cases of rheumatic polyarthritis and disregard those cases presenting the nonarthritic manifestations of this disease.

During the war about 5 per cent of the men in the draft were excluded because of organic heart disease. Combined school, industrial and insurance statistics show that from 2 to 25 per cent of the population have some form of organic heart disease. Emerson⁷ stated that not less than 1 per cent of the population requires care for some class of heart disease. It is thus evident that as an economic load heart disease at least equals in importance that of tuberculosis.

Autopsy Statistics Cabot⁸ presents statistics from 4,000 autopsies (a total of 4143 cardiovascular lesions in 1906 persons) which show that rheumatic valvular heart disease is twice as common as syphilitic aortitis and five times as common as syphilitic valvular disease. Mitral stenosis, alone or combined, is three times as common as all other rheumatic valve lesions combined. Mitral stenosis uncomplicated is two times as common as any other single valve lesion. Figures show a falling off in the amount of fatal rheumatic heart disease but show no falling off in the amount of pericarditis. The age at the time of death is most often thirty to thirty-nine years.

The incidence of family infection in rheumatic fever is about that of tuberculosis. St Lawrence⁷ showed that in 50 per cent of families two or more persons had rheumatic infection. Faulkner and White⁹ gave 35.5 per cent as a comparable figure. Swift⁸ stressed the house and person to person infection. While there is usually a low grade of contagiousness this disease may assume epidemic proportions.^{11,12} It appears probable that the lungs serve either as a portal of entry for rheumatic infection or as a source of reactivation. Numerous authors have called attention to the relationship at times observed between bronchopneumonia and rheumatic carditis.

ASSOCIATED CONDITIONS

Coburn¹³ in an excellent monograph considers the relationship existing between rheumatic fever and upper respiratory tract infections, both in the initial and recurring attacks. Having noted that rheumatic fever is extremely uncommon in the tropics, he transported ten patients with active rheumatic fever from New York to Porto Rico for a period of six months, so far as possible avoiding any change in the management of these patients other than that of climate. In brief, his results showed that the rheumatic process, severe in New York, subsided during three months in the Tropics, disappeared clinically during six months in the Tropics, and evidenced itself with sudden reappearance of symptoms in some instances shortly after the return of these patients to New York. These observations strongly suggest that the rheumatic state was influenced by the change in environment.

Nichol,¹⁴ in a study of the incidence in Florida of two common diseases encountered in the colder states of this country, namely, rheumatic fever and pneumonia, notes an extremely low incidence of rheumatic fever, whereas that of pneumonia is relatively much higher. "Among 31,000 hospital records there were 10 cases of rheumatic fever or chorea and 152 cases of lobar pneumonia." He believes that we should find among children born and reared in this area practically no heart disease of rheumatic origin.

The weight of evidence seems to indicate that rheumatic fever is most frequently encountered in the temperate countries, but Paul¹⁵ furnishes some interesting exceptions to this rule. For details as to the theories and known facts relating to the geographical distribution and of family and environmental influences associated with rheumatic fever the reader is referred to his recent report.

Rheumatic fever is especially invasive in early to middle childhood and at this age period when its onset is especially insidious, the visceral phenomena (carditis, etc.) are more frequently observed than at a later period when arthritic phenomena predominate. Puberty appears to be a critical period, but following this the tendency to rheumatic infection diminishes. Girls appear to be definitely more susceptible to rheumatic carditis. In addition to rheumatic fever, chorea, tonsillitis and other types of streptococcal infection of the respiratory tract, scarlet fever and puerperal sepsis have been considered to bear an etiological relationship. Swift¹⁶ especially stresses the importance of streptococcal focal infections (tonsillitis,

sore throat, pyorrhea and apical abscesses) as predisposing factors in rheumatic fever and rheumatic heart disease. It must be admitted, however, that in the majority of cases of focal infection this relationship is assumed rather than proved

Newsholme, in England, showed the greatest number of cases to occur in those years in which the annual rainfall is lowest, while in the United States the disease is most prevalent in the spring months. Against the theory of dampness being a factor is the fact that during the war in France rheumatic fever was noted to be comparatively rare in spite of the exposure in trench life.

Because of the intimate relationship which exists between rheumatic fever and chorea, it is generally assumed, though by no means proven, that the infectious agent is identical. Riesman and Small¹⁷ include chorea as a manifestation of rheumatic fever. The incidence of the appearance of rheumatism antecedent to chorea varies according to different authors from 9 to 71.5 per cent. In Oxford Medicine¹⁸ appear the following figures on the incidence of rheumatism antecedent to chorea.

Apt and Levinson	143 cases	9 per cent
Branson	67 cases	71.5 per cent
Collective Investigation		
Committee of B M A	439 cases	26 per cent
Osler	554 cases	15.8 per cent
		had acute or subacute joint swelling either preceding or subsequent to chorea

While these figures appear contradictory, it must be borne in mind that there is often great difficulty in determining the presence of fleeting articular involvement, that vague joint and muscle pains are not always sus-

ceptible of exact classification and that the rheumatic infection may not become manifest until after the chorea has passed away. Nodules occurring in the vicinity of joints in chorea are, according to Kaufmann,¹⁹ analogous to Aschoff bodies and hence furnish further evidence of the etiological unity of these two diseases.

It seems desirable to stress this relationship of chorea and rheumatic heart disease since not all pediatricians appear to recognize it. Waggoner²⁰ in a recent article on chorea barely mentions this relationship and in his consideration of treatment makes no mention of the prevention of heart disease in chorea or of the care of the choreic cardiac patient. In the present state of our knowledge it is wise to search diligently for a history of frank or masked chorea in childhood in connection with the obtaining of the history of any cardiac patient.

BACTERIOLOGY

No attempt will be made to review all of the literature relating to this phase of the subject. There appears, however, to be a unanimity of opinion that some form of streptococcus, or perhaps many forms are capable of

producing rheumatic fever and its sequel, rheumatic heart disease. The work of Small^{21,22} and his associates has attracted considerable attention in recent years, although this work has not been substantiated by other work-

ers He presented the *Streptococcus cardioarthritides*, which possesses a specific immunity identity Isolated first from the blood of the rheumatic fever patient, then from the throat, it is claimed that it is capable of producing characteristic arthritic and cardiac pathology in rabbits, including Aschoff nodules, and that a specific serum can be prepared with it

The organism is a spherical Gram-positive coccus which in fluid medium yields diffuse growth and shows short chain formations It is readily stained by the ordinary aniline dyes It is nonmotile, aerobic and facultatively anaerobic Neither flagella, spores, nor capsules are demonstrable It is of rather constant, uniform size, varying from 0.7μ to 1.2μ in diameter The optimum temperature for growth is 37°C , but growth at low temperatures occurs Regarding sources of *Streptococcus cardioarthritides*, Small in his recent report mentioned only the throat and blood and evidently doubted his former finding from feces He stated that the organism is found regularly in throat culture in cases of rheumatic fever or chorea and has been obtained in three instances from blood in rheumatic fever Cultures should not be made from the crypts of intact tonsils, since these usually show *Streptococcus viridans*, *hemolyticus*, etc, but from the superficial sites in the pharynx—pillars, uvula and soft palate

That other organisms than *Streptococcus cardioarthritides* may be the cause of rheumatic fever and the usual manifestations of rheumatic heart disease was shown by Tredway,²³ who reported the case of a boy of $13\frac{1}{2}$ years who had had two previous attacks of

rheumatic fever with carditis In the third attack there was a mild pharyngeal infection with a septic temperature running to 103° The blood culture showed *Streptococcus viridans* on three occasions Later there was pericarditis and effusion Rheumatic nodules were noted at the end of the twelfth week and were present only on the scalp There were no petechiae or other evidences of emboli The only joint involvement was in the left metacarpals and left shoulder for but four days The reasons given for reporting were the unusual blood findings, the absence of joint symptoms, except as above, and pericarditis with effusion Small²⁴ pointed out that from the clinical standpoint confusion has arisen in the differentiation of rheumatic endocarditis and bacterial endocarditis, particularly in the transition stages of the former into the latter A streptococcus obtained in the blood culture of a patient might arise from either the one or the other of these conditions

Clawson²⁵ tabulated the bacteriological results of blood, joint and pericardial exudate cultures as reported by various workers and states, "The conclusion to be drawn from the findings of the various workers on the basis of morphologic, cultural and immunological characteristics is that the group of streptococci isolated from cases of rheumatic fever cannot be considered a specific one, but that it represents a heterogeneous group, generally green-producers on blood agar, with moderately low virulence"

Cecil,²⁶ et al, found a streptococcus—usually *viridans* in type—in the blood and joints of a high percentage of rheumatic fever patients They

noted, however, that indifferent or even hemolytic streptococci may occur.

In addition to our lack of accurate knowledge as to the causative organism, we are likewise uncertain as to whether there is direct bacterial invasion in all cases, or whether there is simply a local tissue reaction, allergic in nature, to toxins produced at some distant bacterial focus. Comparative studies of rheumatic fever, tuberculosis and syphilis suggest that in the former, as well as in tuberculosis and syphilis, there is an allergic factor. Swift²⁷ demonstrated that the intradermal injection of living streptococci into rabbits produced not only an immediate inflammatory reaction, but in addition a later but milder inflammatory reaction, which occurred in the absence of living streptococci in the involved tissues. He also showed hypersensitivity of the skin of rheumatic fever patients to streptococci, which he interpreted as a specific allergic manifestation. Kinsella²⁸ has cited another example of allergy which apparently occurs in gonorrheal rheumatism. He pointed out that gonorrheal arthritis never occurs in the early state of the urethritis but after several weeks or months and then apparently associated with some other condition which permits a blood invasion. Then we have a totally different response on the part of the body to bacterial invasion.

PATHOLOGY

Limitation of space prevents any extensive consideration of pathological changes, but it should be stressed that rheumatic carditis is usually a pancarditis, that while the acute involvement of the pericardium and myocar-

dium is usually transient and clears with little or no permanent impairment of these tissues, that of the endocardium usually leads to deformity with resultant hindrance to the filling and emptying of the heart chambers—a condition which secondarily leads to muscle damage.

Lasèque²⁹ wrote, "Rheumatism licks the joints, the pleura and meninges but bites the heart."

No attempt will be made to present a systematic description of the pathological changes in rheumatic heart disease, but in the course of this review certain investigations and ideas presented by the various authors were sufficiently striking to merit comment. Reid³⁰ classified pathological lesions in rheumatic fever as exudative and proliferative, the former changes are found in the joint and serous cavity involvement, the latter in the endocardial and myocardial changes and in the subcutaneous nodules which so frequently accompany this disease.

The two working theories as to the cause of valvulitis are: (1) That trauma of contact of the valve cusps at the line of closure resulted in the lodgment of organisms at this point with subsequent formation of vegetations, (2) That bacteria in the blood stream lodge as emboli in normal capillaries which occur in the valve leaflets. Kerr³¹ on an experimental basis concludes that both of these factors are operative in the production of valvulitis.

Opposed to the usual opinion Crummer³² stated that mitral insufficiency (organic) is one of the least frequent valve defects. But Kaufmann¹⁹ wrote, "Mitral lesions, chiefly insufficiency, constitute two-thirds of all valvular

lesions.' These figures are drawn from autopsy findings. Another interesting note regarding rheumatic valvulitis is that of Cabot,³³ who stated that he had never seen a proven case of tricuspid valvulitis, although Libman³⁴ and Thayer³⁵ have shown its occurrence in 44 and 66 per cent of their cases respectively.

The infrequency of early right sided lesions may be due to the fact that in early life the blood supply to the right heart is comparatively better than to the left.

The most commonly mentioned myocardial lesion is that described by Aschoff—the Aschoff nodule, a sub-miliary collection of large spindle-shaped or branching cells containing large, at times multiple, nuclei. These giant cells, usually grouped in a radiating or fan-like arrangement and occurring in the interstitial tissues, are sub-endocardial and usually perivascular. While this is mainly a proliferative reaction, there may be associated a varying number of polymorphonuclear leucocytes, lymphocytes, eosinophiles and plasma cells. The centers of these nodules undergo necrosis and may later become completely fibrosed. When these occur in the interventricular septum there may be serious involvement of the conduction system with varying degrees of block resulting. Aschoff and others considered these to be pathognomonic of rheumatic myocarditis, but in the past decade groups of giant cells, which could not be readily differentiated from the Aschoff body, have been occasionally demonstrated in other conditions, in general in infections due to streptococci of low virulence. It is thus apparent that while in rheumatic carditis

there is a tissue reaction which is usually characteristic of the disease, the finding of these bodies—in the absence of other evidence—must not be accepted as proof of the existence of rheumatic myocarditis.

Von Glahn³⁶ feels that changes in the left auricular endocardium, previously described by McCallum, are as distinctive and characteristic as the Aschoff bodies. These changes consist of irregular furrows and ridges on the endocardium which terminate at the line of closure of the mitral valve leaflet. In these are found polymorphonuclear leucocytes, small and large mononuclears and wandering cells—a cell group with none of the characteristics of the Aschoff bodies.

As an explanation of the absence of mitral stenosis in advancing rheumatic carditis Smith and Sutton³ stated, "Fibrosis of the mitral valve does not always cause narrowing of the channel because the walls of the ventricle become weakened by the lesions in the musculature, so that the ventricle and the auriculoventricular rings become stretched. In spite of the cicatrization, the mitral channel is thus often held open, making the opening larger than normal and allowing regurgitation." Later in discussing mitral insufficiency they state that the early mitral insufficiency is due less to the condition of the valves than to the myocardial factor which causes muscular relaxation, permitting stretching of the rings.

The earlier descriptions stressed the importance of valvular lesions and of the Aschoff nodule as an evidence of the myocardial lesion, but other studies, notably those of Klotz,³⁷ have shown that certain portions of the

arterial system are as frequently attacked in rheumatism as is the musculature of the heart. Klotz, Allbutt,³⁸ Von Glahn⁴⁰ and others stressed the importance of aortitis, aneurism, pulmonary artery lesions similar to those in the aorta, and peripheral vascular lesions in rheumatic fever. Discussing aortitis, syphilitic and rheumatic, Klotz noted, "In syphilis the disease rarely comes to a standstill, at least in so far as the recognized and studied cases indicate." In rheumatic disease of the aorta the process usually comes to an end spontaneously, but always predisposes the involved areas to recurrent attacks. Regarding the frequency of aortitis in rheumatic fever he stated, "The almost constant presence of some inflammatory reaction in the ascending limb of the aorta should be recognized as an associated condition in this disease."

Allbutt³⁸ stated that rheumatic aortitis is not rare but usually unrecognized; being usually superficial, it is often painless and in most cases it arouses no symptoms. Numerous other authors have cited cases of aortitis and aneurism in children, of rheumatic origin and often associated with typical anginal symptoms.

Myocarditis may occur in the absence of demonstrable valvulitis. Cabot³⁹ reported the case of a boy of fifteen who had a fibrous rheumatic myocarditis, particularly of the left auricular wall. There was no acute endocarditis but fibrous thickening of the mitral and tricuspid valves without stenosis or noteworthy insufficiency. Dr. T. B. Mallory stated that this was the second case seen in four months—a pure rheumatic myocarditis.

Mackenzie,⁴⁰ in discussing peri-

carditis, stated that when pain is present it will be found invariably that there is evidence of myocardial affection. Swift⁸ stressed the fact that pericarditis is not of itself painful. Regarding the frequency of myocardial involvement there are varying opinions. Aschoff bodies, the accepted pathological evidence of myocardial involvement, are demonstrated frequently at autopsy, but whether they frequently or always occur with the first attack is a question which has caused considerable controversy. Allbutt²¹ wrote that the myocardium is probably involved in every case—the endocardium and then pericardium coming next in order. The first symptom is usually palpitation and stabbing pain over the heart or a feeling of tightness or oppression in the left breast.

Coronary changes have not been considered of importance in rheumatic heart disease until very recently. Perry,⁴¹ in 1930, reported eight autopsies upon cases of rheumatic fever carditis showing coronary changes. This study was incited by the findings at the autopsy of a child who during life suffered from typical anginal pain in the course of a severe rheumatic carditis. The main branches of the coronary arteries showed severe intimal thickening, with a considerable reduction in size.

Any discussion of coronary and myocardial changes in rheumatic fever and rheumatic heart disease would be incomplete without a reference to the electrocardiographic evidence of these changes. Peel,⁴² Wyckoff,⁴³ et al., have noted changes in the T wave and in the conduction time. Wyckoff and his associates noted wide and inconstant variations in the A-V conduction

time and that there is no proof that they are influenced by salicylate therapy

Master⁴¹ reported the frequent finding of flat T waves in one or more leads and noted that in subsequent observations these waves may become inverted, or if taken at a later period may again become upright, indicating in either case a progressive myocardial change. Slater,⁴⁵ in a recent report, presented three cases which showed inversion of the T waves occurring in the course of rheumatic fever. These were all in adults, suggesting a greater arterial vulnerability. This author believed that this represents a coronary occlusion, not necessarily due to thrombosis, "but that the specific lesion in the vessel may be the site of considerable edema, as in any exudative condition, and that this may account for the closure."

Certain authors⁴³ have attempted to formulate diagnostic criteria based upon the type and degree of T wave changes. A review of the material in the Colorado General Hospital and of cases seen in private practice fails to substantiate these claims. For the present it would seem preferable to depend upon evidence of arrhythmias, of conduction disturbances between the auricles and ventricles or within the ventricles, and abnormal preponderance of one side of the heart. Not infrequently the electrocardiogram will furnish the only sign of cardiac involvement—in fact, cases have been reported in which these changes have occurred before any other evidence of rheumatic infection had become manifest.

Pericarditis Cabot⁶ stated that the pericardium in childhood is more

sensitive than in later life, hence pericarditis is more frequently encountered at this period. Allbutt,⁴⁶ writing in Oxford Medicine, stated that the incidence of pericarditis in rheumatic fever is about 10 per cent. He had the impression that pericarditis is less frequent in rheumatic fever than a generation ago and suggested that salicylates may have more of a protective influence in pericarditis than in endocarditis. Pericarditis may precede any grade of arthritis in the young, in older cases it is found only in the severer forms. Combs⁸ stated that 53 per cent of all cases of all ages show pericardial changes at autopsy—though not clinically. Rheumatic pericarditis is never suppurative. Regarding pericardial effusions, Mackenzie⁴⁰ has never found any serious embarrassment of the heart from even extensive effusions.

The question as to the frequency of carditis in rheumatic fever has attracted considerable attention. Swift⁸ stated, "The infection in childhood leads more frequently to cardiac sequelae, indeed it is often questionable whether the first tissue to be attacked by the virus in the early years of life is not that of the heart." In a series of eighty-one rheumatic fever patients⁴⁷ he obtained electrocardiographic evidence of functional cardiac disturbance in over 90 per cent. Wilson,⁴ et al., stated, "The heart is probably always effected at the onset of this [rheumatic fever] disease." White¹⁰ stated, "The rheumatic infection usually or always involves the heart."

All recognize the tendency of mitral stenosis to remain "silent" throughout many years after the acute rheumatic attack. Yet there must in many cases

be some progress during this interval Riesman and Small¹⁷ conclude that the cardiac involvement is part and parcel of the rheumatic process and is no more a complication or a sequela than is involvement of the shoulder joint a day or two after that of the knee joint. Certain other authors state that they have never seen a child below ten years of age suffer from rheumatic fever without involvement of the heart. Mackie⁴⁸ analyzing 366 cases of rheumatic fever found that at five years of age 61.5 per cent, and at ten years 78 per cent, presented evidence of carditis in the first attack. Washburn² in a recent paper read before the Denver County Medical Society stated that he was certain carditis did not always occur, that he had followed a considerable number of children in which there was never any evidence of carditis. Certainly the failure to demonstrate carditis during an attack is insufficient proof of an intact heart since the murmurs of endocarditis may only be demonstrated months after an attack.

Von Glahn³⁶ presented some interesting figures relative to the possible duration of active rheumatic carditis. In his series of 109 cases he noted that 35 of the cases had a free interval from arthritis of one to thirty-eight years, yet had acute rheumatic disease at the time of death, and that in 50 per cent of those with arthritis, acute rheumatic cardiac lesions may be found when there has been freedom from joint attacks for intervals as long as thirty-eight years. In other words, there is either reinfection without joint symptoms, or persistence of the infection in masked or latent form—often over many years.

With each decade of life there is

less liability of permanent cardiac damage in rheumatic fever, which means that for the prevention of rheumatic heart disease the early attacks of rheumatic fever must be prevented. Typical acute rheumatic fever is rare after forty, for at this period of life polyarthritis is apt to be preceded by a "cold" or influenza, and the cardiac picture is quite different from that associated with childhood rheumatism.

As a means of prevention of rheumatic fever in childhood, tonsillectomies have been extensively performed on the theory that the tonsils represent the primary site. Certain it is that the incidence of rheumatic fever is greatest in the young where there is an excess of lymphoid tissue. Swift's series shows that tonsillitis is an antecedent of rheumatic fever in about 50 per cent of cases. Kaiser,⁴⁹ in a study of 439 rheumatic fever children, found that nearly twice as many children developed the first attack of rheumatism when the tonsils had not been removed and that after tonsillectomy recurrent attacks occurred 10 per cent less frequently, but in general the results of tonsillectomy have been disappointing in the prevention of rheumatic carditis. A tonsil stump may retain sufficient infection to cause a recurrence or an initial rheumatic infection. Riesman and Small¹⁷ obtained cultures of *Streptococcus cardioarthritides* from the "superficial sites in the pharynx" and suggested that surgical removal of the tonsils will not eradicate these foci. Katz⁵⁰ described these foci as "post-operative foci." It is probable that the tonsils are only one of the portals of entry and that any infection of the up-

per respiratory tract may prove equally responsible

At the present time we have no certain method for the prevention of rheumatic infection in childhood, but much can be accomplished toward the prevention of cardiac sequelae if the earliest manifestations of rheumatic carditis are recognized. Childhood rheumatic carditis may occur in a mild form with symptoms only of undue fatigue, pallor, loss of weight and appetite, or failure to grow and gain in weight, and only slight dyspnea on exertion. On examination, aside from moderate anemia and undernutrition, with slight increase in pulse rate, there may be no demonstrable signs. These cases present a striking similarity to tuberculosis. In connection with the milder symptoms the frequency of effort syndrome at puberty should be recalled.

When rheumatic fever is denied, search for a history of chorea, frequent tonsillitis, fleeting growing pains and purpura. The frequency and severity of infantile and adolescent pneumonia, pleurisy and painful conditions of the chest may be evidence of earliest heart disease.

CLINICAL PICTURE

In any discussion of the clinical picture of rheumatic heart disease it is necessary to stress first some of the variations in the clinical picture of acute rheumatic fever. The classical picture of acute rheumatism is too well known to require repetition but some of its variants may deserve mention. The migratory arthritis may be absent. Von Glahn³⁶ in a series of 109 cases found 41 "who never had arthritis." There may be only pain and tenderness without swelling. In chil-

dren the disease tends towards chronicity while in adults the attack is characterized by its explosiveness. According to Swift,⁸ "In the adult the arthritis and visceral complications, if they occur, are usually seen within a short period of a few weeks—in children, on the other hand, although the disease is ushered in by an acute onset, the various groups of symptoms may make their appearance months apart." In the latter, nervous symptoms, chiefly the manifestations of chorea, are likely to occur. These may consist simply of nervousness, irritability and clumsiness, or the jerking movements typical of the disease. Frequently observation over a considerable period is necessary in order to establish a diagnosis.

The importance of pulmonary and pleural involvement in rheumatic carditis should be stressed. A left sided fibrinous pleurisy (near the heart) occurs in from 5 to 10 per cent of cases. Pneumonia may mask the picture of rheumatic fever, a condition I described in 1928 under the title of Occult Rheumatism.⁵¹ There has been some discussion as to the occurrence of a specific rheumatic pneumonia. Aschoff bodies have been described³ in the pulmonary arteries and other characteristic changes in the arterioles of the lung. These pulmonary changes occur more frequently in cases of pancarditis, although they are described as occurring sometimes independent of arthritis or carditis, as in a case reported by myself.⁵¹ It is well to consider this possibility with the occurrence of a "wet pleurisy", for this may be due to rheumatic fever as well as tuberculosis. Paul⁵² has recently published a comprehensive review of

the literature on pleural and pulmonary lesions in rheumatic fever

Subcutaneous nodules occur chiefly in children, rarely in adults. Three types are described: (1) Miliary, in tendons and sheaths; (2) Medium-sized, in broad tendons that pass over joints and at insertions; and (3) Large, over bony surfaces beneath the skin. Nodules usually occur in severe forms of rheumatic infection and have been thought to suggest a poor prognosis, but recently White¹⁰ suggests that they may indicate a favorable reaction. These nodules may be noted late and may not occur on extremities, as in the case of Tredway²³ previously cited, in which they appeared at the end of the twelfth week and were present on the scalp only.

The rash in rheumatic fever (*Erythema multiforme*) may come in crops with each new involvement of the joints. This occurs at some period in about 15 per cent of the cases, but this sign, as well as the nodule, is less frequently observed in this country than in England. Less frequent skin manifestations are *erythema nodosum*, *urticaria*, *purpura* and *petechial hemorrhages*. These are the most frequent symptoms of heart invasion—only rarely are pain and dyspnea complained of during the acute stage. Later, if symptoms occur, they are those of congestive failure.

Disturbances of Rhythm Swift⁸ states that 20 to 30 per cent have transient conduction disturbances. Auricular and ventricular premature contractions are frequent. Auricular fibrillation and flutter, also heart block, are serious complications. Mackenzie¹⁰ cites as a rarity a case of auricular fibrillation in a child of five

years suffering from rheumatic fever. Associated with these, Neuhof⁶¹ describes "thumpings" occurring with a normal rate, thought by him to be due to "abnormally strong ventricular contractions", and describes also sensations of weight and pressure on the chest not unlike the anginoid pains described by Allbutt. These precordial sensations, except as found in the psychoneurotic type of patient, surely indicate myocarditis or the aortic involvement described by Allbutt.

Pulse The pulse without heart complications is proportional to the temperature. A high pulse after the disappearance of arthritis is strong evidence of carditis. A slight acceleration of the pulse may precede by several days the physical signs of endocarditis.

Murmurs Prior to the appearance of a murmur the heart sounds may be muffled due to edema of the valves or may be increased due to ventricular hypertrophy. A systolic murmur without persistent cardiac enlargement and regardless of transmissions is insufficient evidence of organic mitral insufficiency—for even functional murmurs may be heard in the back.

Conclusive signs of stenosis only appear after fibrosis and contraction, which is months after the initial infection. Mitral stenosis, rheumatic in origin, may show only a systolic murmur while the heart is beating slowly. If the rate be increased by exercise or by some drug (amyl nitrite) a diastolic murmur may be heard, likewise a mid-diastolic murmur may be heard only in the recumbent posture. In the absence of a murmur in

diastole, early, mid-, or late, or a definite presystolic murmur, the need of special investigation should always be suggested by a history of chorea or rheumatic fever when there is an unusually sharp first sound, a systolic murmur which begins abruptly, an increased or doubled pulmonary second sound—especially when the second sound at the apex is diminished in intensity—and by the presence of auricular fibrillation or a break in compensation not due to some other cause. Any loud apical systolic murmur in childhood warrants a careful search for signs of mitral stenosis.

Pericarditis This is not of itself painful, with the onset of temperature and pulse increase one should look for a rub, but because of the evanescent character of pericardial rubs the failure to demonstrate one does not preclude pericarditis.

Cardiac hypertrophy, disproportionate, or not explained by other lesions, suggests adhesive pericarditis. An absence of shifting with postural changes noted in the fluoroscope and electrocardiogram are further evidences of adherent pericardium, but some of the other signs usually associated with adherent pericardium may have a different cause. Systolic retraction at the apex and sternum may be due to right ventricular hypertrophy. Pulsus paradoxicus (waxing and waning with respiration) is present in myocardial insufficiency and in many normals. Diastolic collapse of cervical veins (Friedrich) is not characteristic, since it is seen also in auricular fibrillation. Broadbent's sign may be due to an enlarged heart pulling on its attachments to the diaphragm.

Fever A temperature of 102° to 104°, if this increase occurs without new joint involvement, suggests visceral involvement. Light fever for weeks or months after the acute symptoms is strong evidence of cardiac involvement, especially when accompanied by leucocytosis*. The lesion may be in the myocardium or mural endocardium.

Sudden pallor, restlessness and nausea, pulse increase with albuminuria and liver enlargement in the course of, or subsequent to, rheumatic fever strongly suggest shock due to splanchnic dilatation.

PROGNOSIS

This depends upon the age at which the initial infection occurs and the frequency of recurrence of rheumatic infection. With a slight lesion, protection throughout life, and luck, the individual may carry a rheumatic valve lesion with very little if any disability and reach the normal life expectancy, but more frequently cardiac sequelae cripple the patient for years before he finally succumbs**. Cohn⁵⁸ stated that an average period of fifteen years

*Recent studies indicate that the sedimentation rate may serve as a useful indication of existing cardiac infection.

**In a recent article Morse⁶⁴ analyzes 100 consecutive cases of acute rheumatic (?) endocarditis, seen in the first attack and followed over a period of 10½ to 26½ years, and comments on the relatively small number of deaths (36), the small number of cardiac invalids (3), and the large number of complete recoveries (61). Of this group of 61 cases who had completely recovered, Morse found 37 in whom the hearts appeared normal on examination. Even allowing for a certain small factor of diagnostic error, this percentage of apparently normal hearts is so striking as to merit comparable studies by other competent observers.

elapses between the initial attack of acute rheumatic fever and the death of the patient from the resulting heart disease Christian⁷⁴ places a comparable figure at twenty years and White¹⁰ at ten to twenty years. In adult life there is much less likelihood of additional rheumatic valve involvement due to recurrent rheumatic infection, but far greater danger of auricular fibrillation, with the frequently resulting congestive heart failure, and of a *Streptococcus viridans* infection as an added insult to the existing rheumatic endocarditis. Patients with aortic valve lesions or mitral lesions which are predominantly regurgitant are somewhat more prone to viridans infection than are those with mitral stenotic lesions. Most important is the certainty of progression in the mitral stenotic lesions. Allbutt states that pericarditis in an adult always carries with it a poor prognosis.

COMPLICATIONS

Congestive heart failure, auricular fibrillation and subacute bacterial endocarditis (*Streptococcus viridans*) constitute the most important complications. Congestive heart failure occurs in at least two-thirds, fibrillation in one-fifth and viridans infection in 4 per cent of all cases of rheumatic carditis according to figures furnished by White¹⁰.

TREATMENT

Salicylates Regarding the treatment of rheumatic fever Swift⁸ advised us to obtain the maximum effect of salicylates to the point of beginning toxicity, rest one day and then give a smaller dose. Crummer³² felt that cases properly treated show less tendency to pericarditis and "endo-

cardial changes" and tend to earlier stabilization. Leech⁵¹ believed there is a definite advantage in giving daily rations of salicylates to children who represent actual or potential instances of rheumatic heart disease. There is no evidence of any effect of the drug on the slowly progressive development of mitral stenosis.

While Mackenzie¹⁰ taught that there is a specific action of the salicylates on the rheumatic heart, the general opinion appears to be that this drug is less efficient in its action on the heart than on the joint tissues. This difference in response on the part of different tissues has some experimental basis. Hagebush and Kinsella⁵⁰ showed that the allergic dermal reactions produced in rabbits in the course of chronic focal streptococcal infection could be entirely prevented by salicylates, while the vascular lesions remained unaltered. Small⁵⁷ stated that there is a difference in response to salicylates in the proliferative (heart) and exudative (joint) lesions. Wyckoff⁴³ showed that salicylates have no effect on the A-V conduction time. It would seem that the prophylactic use of salicylates during any acute respiratory infection might be of value in reducing the number of cases of rheumatic fever and hence of rheumatic carditis. Quite recently it has been shown⁵⁸ that by the simultaneous administration of magnesium sulphate or chloride (grams 2 to 4) and salicylates there is a distinct augmentation of the effect of the latter. This process is described as potentiation and is comparable to that observed when magnesium salts are administered with morphine.

Digitalis Schwartz⁵⁹ stated that in

childhood nausea and vomiting occur as a late manifestation of digitalis action, whereas slowing of the sinus rate occurs early but is a transitory phenomenon, never lasting more than four to seven days. If digitalis is pushed further, block occurs. He believed that nausea and vomiting cannot be safely used as criteria of digitalization in rheumatic valvular heart disease with failure. Schwartz also said that digitalis in adequate doses can produce both the transient and permanent forms of auricular fibrillation in children with heart disease. This may be an early manifestation of its toxic effect and may result fatally. He concluded that digitalis is contraindicated in children with rheumatic fever and signs of cardiac insufficiency. Allbutt³³ advised against digitalis in the acute stage.

Levy and Golden⁹⁰ suggested roentgen therapy in rheumatic carditis. They believed this modifies the lesions, basing their opinion upon alterations in the form of the electrocardiogram, and felt that in thirty cases of rheumatic heart disease the clinical course was apparently influenced in twenty-one. In their article I find no mention of similar electrocardiographic observations in a control series—as in a series of noncardiac cases—a point of considerable importance since roentgen exposure is known to cause changes in the heart muscle.

Clawson²⁵ showed that "lesions similar to those found in rheumatic fever can be produced in animals" by the injection of streptococci and that animals so sensitized can be protected from these rheumatoid lesions by intravenous streptococcus vaccination.

He concludes that since rheumatic fever patients are hypersensitive to streptococci, intravenous vaccination with streptococci "may be indicated in acute rheumatic fever."

Swift,¹⁸ et al., in a recent article presented a very complete review of vaccination with streptococci in rheumatic fever. They advanced a working hypothesis which assumes hypersensitivity to streptococci associated with continuous or repeated low-grade focal infection. If at any time an acute infection supervenes—as tonsillitis, or sinusitis—this hypersensitivity increases. They stated, "These irritants appear to attack those mesenchymal tissues most subject to physiological trauma, hence lesions commonly occur in such constantly moving structures as joints, tendons, heart and blood vessels." They further stated, "In patients with active disease, both febrile and focal reactions following vaccination have many resemblances to true rheumatic relapses and that these can either be prevented or terminated by anti-rheumatic drugs, is highly suggestive", and that "the sensitization responsible in part for the pathogenesis of rheumatic fever was induced by strains closely related to hemolytic streptococci."

Discussing the advantages of intravenous over subcutaneous vaccination they show that in animals the "injection of streptococcal vaccines into the tissues usually tends to sensitize, while intravenous injections tend to diminish the overactivity of hypersensitive tissues, and therefore the logical method would be intravenous inoculation under proper precautions." In addition the local reactions about the

site of subcutaneous vaccination with streptococci are often so intense that patients are unwilling to have them repeated. Intravenous injections, on the other hand, are free from local reactions, and most patients are willing to continue them for a full course, hence, from both a theoretical and practical point of view, the intravenous route is the one of choice. This form of treatment Swift considered especially applicable to two classes of patients: (1) Those with a continuing low-grade infection, and (2) those temporarily free from symptoms, but in whom relapses may reasonably be expected. They seem to show a distinct result from the intravenous administration of a vaccine made from hemolytic streptococci. "In about four-fifths of the patients increasing tolerance to the vaccine was accompanied by improvement."

Discussing treatment by means of vaccines, anti-sera and soluble products of bacteria, Small⁶⁷ stated that there are three main methods of attack upon the tissues in rheumatic fever: (1) Local growth of streptococci, (2) General toxic effect of streptococci, (3) Other bacterial products distributed from a focal source and capable of inducing and maintaining the allergic state. Probably these seldom act singly. Small's working hypothesis assumed that the visceral (vascular and cardiac) lesions on the one hand and the joint lesions on the other are caused by a different mechanism. The former are due to a specific endotoxin, the latter to the establishment of hypersensitiveness to a protein fraction contained in numerous streptococci, an example of the production of a specific allergin of di-

verse biologic origin. "The problem in therapy of acute rheumatic fever appears to be that of complete neutralization of the toxic factor by a specific antiserum without passively transferring to the patient hypersensitization to the protein antigen common to different streptococci." The focal reaction in joints following the administration of Small's antiserum is a manifestation of this passive transfer of allergy, therefore the protein fraction must be removed. To accomplish this he uses his "soluble antigen."

In the treatment of rheumatic fever and its visceral complications Small²² reported results in 1928 as follows:

There were prompt beneficial effects in 251 patients with chorea and acute rheumatic fever. In these were acute arthritis, endocarditis, myocarditis, pericarditis, pleuritis, pneumonitis and subacute nodules. In chorea the twitchings subside promptly and usually disappear in one week. This serum should be used as early as possible and is not contra-indicated by carditis. If the patient is sensitive to horse serum Small furnishes a bovine antiserum following the administration of which severe urticaria, febrile reactions and arthralgia are less common. Further, to prevent severe reactions, the serum is given in divided doses to patients acutely ill.

Vaccines proved to produce reactions in deep seated rheumatic infections, so were discontinued in favor of soluble antigen, but this was not used except as a followup treatment after the antiserum, and as a prophylactic it is again given in the spring and fall for several years, giving six to twelve injections with each series. Small

especially emphasizes the importance of avoiding noteworthy reactions

From the foregoing it will be evident that, although a great deal of work has been done along the line of biological treatment of rheumatic fever in its various manifestations, there is no uniformly accepted biological treatment

Rest The chief method of therapeutic attack in rheumatic carditis has been left to mention last. Complete bed rest at the earliest appearance of any manifestation of rheumatic fever and until all evidence of any type of acute rheumatic involvement is past will offer the greatest assurance of prevention of extension of the process to the heart, if this be possible, and if not will furnish the greatest surety of a limitation of that process and a minimum of cardiac damage

Rheumatic carditis ordinarily dates from childhood rheumatism. Every rheumatic child, if not actually, is po-

tentially a cardiac patient. Even in the absence of demonstrable carditis the child with rheumatic fever or chorea should be treated as a cardiac patient, which means primarily rest over a long period. With such a treatment the physician will cure many early cases of cardiac rheumatism and, if not so fortunate, will at least prevent many of the sequelae which determine whether the child should enjoy comparative health or invalidism

Prevention of rheumatic carditis The foregoing paragraph probably embraces all that we know definitely regarding the subject. Rheumatic fever appears to be a communicable disease with about the same tendency to family infection as has tuberculosis. Presumably the prevention of upper respiratory tract infection will in the future materially reduce the incidence of rheumatic fever and rheumatic heart disease

REFERENCES

- ¹STOKES, WILLIAM. Diseases of the heart and aorta, 1854, Hodges and Smith, Dublin
- ²WASHBURN, A. H. Prevention of heart disorders in early life, Colorado Med., 1931, xxviii, 338-345
- ³SMITH, C. H., and SUTTON, L. P. Heart disease in infancy and childhood, Clinical pediatrics, 1930, Appleton, New York
- ⁴WILSON, M. G., LINGG, C., and CROXFORD, G. Statistical studies bearing on the problems in the classification of heart disease, Am Heart Jr, 1928, iv, 164-196
- ⁵EMERSON, HAVEN. Heart disease—communicable? curable? preventable? Survey, 1924, lvi, 113-118
- Prevention of heart disease, a new practical problem, Boston Med and Surg Jr, 1921, clxxxiv, 587-607
- ⁶CABOT, RICHARD. Facts on the heart, 1926, Saunders, Philadelphia
- ⁷ST. LAWRENCE, W. The family association of cardiac disease, acute rheumatic fever and chorea, Jr Am Med Assoc, 1922, lxxix, 2051-2055
- ⁸SWIFT, H. F. Oxford medicine, 1921, Oxford University Press, New York, v 11-38
- ⁹FAULKNER, J. M., and WHITE, P. D. The incidence of rheumatic fever, chorea and rheumatic heart disease with special reference to its occurrence in families, Jr Am Med Assoc, 1924, lxxxiii, 425-426
- ¹⁰WHITE, P. D. Heart disease, 1931, Macmillan Company, New York
- ¹¹BOAS, E. P., and SCHWARTZ, S. P. The modes of infection in rheumatic fever, Am Heart Jr, 1927, ii, 375-386

- ¹²HATHAWAY, J C Rheumatic fever communicable disease, Minnesota Med 1930, xiii, 37-40
- ¹³COBURN, A F Factor of infection in the rheumatic stage, 1931, Williams and Wilkins, Baltimore
- ¹⁴NICHOL, E STERLING Rheumatic fever and lobar pneumonia notes on occurrence in Southern Florida, Jr Florida Med Assoc, 1931, xvii, 366-368
- ¹⁵PAUL, J R Epidemiology of rheumatic fever, a preliminary report with special reference to environmental factors in rheumatic heart disease and recommendations for future investigations, For the Am Heart Assoc, 1930, Metropolitan Life Ins Co Press, New York
- ¹⁶SWIFT, H F, HITCHCOCK, C H, DERICK, C L, and McEWEN, C Intravenous vaccination with streptococci in rheumatic fever, Am Jr Med Sci, 1931, clxxxii, 1-11
- ¹⁷RIESMAN, D, and SMALL, J C Rheumatic fever—clinical manifestations, etiology and treatment, Ann Int Med, 1929, ii, 637-644
- ¹⁸OXFORD MEDICINE, vi, 939, 1921, Oxford University Press, New York
- ¹⁹KAUFMANN, E Pathology, Reimann's translation, 1929, Blakiston, Philadelphia
- ²⁰WAGGONER, R W Sydenham's chorea, Am Jr Med Sci, 1931, clxxxii, 467-476
- ²¹SMALL, J C Bacterium causing rheumatic fever and a preliminary account of the therapeutic action of its specific antiserum, Am Jr Med Sci, 1927, clxxiii, 101-129
- ²²SMALL, J C Rheumatic fever, Ann Int Med, 1928, i, 1004-1006
- ²³TREDWAY, T P Endocarditis and pericarditis with blood-stream infection of *Streptococcus viridans*, Pennsylvania Med Jr, 1930, xxxiii, 389
- ²⁴SMALL, J C Symposium on rheumatic fever the etiology and specific treatment of rheumatic fever, Atlantic Med Jr, 1928, xxxi, 802-805
- ²⁵CLAWSON, B J Bacteriology of acute rheumatic fever with an experimental basis in animals for vaccine therapy, Minnesota Med, 1931, xiv, 1-4
- ²⁶CECIL, R L, NICHOLLS, E E, and STAINSBY, W J Etiology of rheumatoid arthritis, Am Jr Med Sci, 1931, clxxxii, 12-25
- ²⁷SWIFT, H F, ANDREWS, C H, and DERICK, C L Skin response of rabbits to nonhemolytic streptococci, description of secondary reaction occurring locally after intradermal inoculation, Jr Exper Med, 1926, xlv, 35-53
- ²⁸KINSELLA, R A Present theories concerning the etiology of acute rheumatic fever, Minnesota Med, 1931, xiv, 203-205
- ²⁹LASEQUE, C Études Medicales Du Rhumatisme, 1884, Asselin Cie, Paris
- ³⁰RLID, W D Heart in modern practice, 1928, J B Lippincott Co, Philadelphia
- ³¹KERR, W J, MERTIER, S R, and McCALLA, R L Capillary circulation of the heart valves in relation to rheumatic fever, Trans Assoc Am Phys, 1928, xliii, 213-216
- ³²CRUMMER, LEROY Clinical features of heart disease, second edition, 1930, Paul Hoeber, New York
- ³³CABOT, RICHARD Dyspnea and edema in a child of thirteen, case 16171, Massachusetts General Hospital, New England Jr Med, 1930, ccii, 824-827
- ³⁴LIBMAN, E Characterization of various forms of endocarditis, Jr Am Med Assoc, 1923, lxxx, 813-818
- ³⁵THAYER, W S Notes on acute rheumatic disease of the heart, Bull Johns Hopkins Hosp, 1925, xxxvi, 99-104
- ³⁶VON GLAHN, W C, and PAPPENHEIMER, A M Rheumatic disease of the auricle and blood vessels, Trans Assoc Am Phys, 1928, xliii, 203-212
- ³⁷KLOTZ, OSCAR Arterial lesions associated with rheumatic fever, Jr Path and Bact, 1914, xviii, 259-269
- ³⁸ALLBUTT, SIR CLIFFORD Diseases of the arteries, 1915, Macmillan, London
- ³⁹CABOT, RICHARD Acute arthritis with dyspnea, Case 15371, Massachusetts General Hospital, New England Jr Med, 1929, cci, 535-537
- ⁴⁰MACKENZIE, SIR JAMES Diseases of the heart, third edition, 1913, Froude, London
- ⁴¹PERRY, C B Main branches of the coronary arteries in acute rheumatic car-

- ditis, *Quart Jr Med*, 1930, xxiii, 241-244
 - ⁴²PEEL, A A F Transient inversion of T wave in acute rheumatism with cardiac complications, *Glasgow Med Jr*, 1929, cxu, 291-306
 - ⁴³WYCKOFF, JOHN, DE GRAFF, A C, and PARENT, S Relationship of auriculo-ventricular conduction time in rheumatic fever to salicylate therapy, *Am Heart Jr*, 1930, v, 568-573
 - ⁴⁴MASTER, A M Low voltage in T waves in electrocardiogram, *Am Jr Med Sci*, 1931, clxxx, 211-217
 - ⁴⁵SLATER, S R Involvement of the coronary arteries in acute rheumatic fever, *Am Jr Med Sci*, 1931, clxxx, 203-210
 - ⁴⁶ALLBUTT, SIR CLIFFORD Oxford medicine, 1921, Oxford University Press, New York, ii, 251-284
 - ⁴⁷SWIFT, H F Rheumatic fever, *Am Jr Med Sci*, 1925, clxx, 631-647
 - ⁴⁸MACKIE, T T The prognosis and treatment of rheumatic infection, *Am Heart Jr*, 1927, iii, 31-44
 - ⁴⁹KAISER, A D The relation of the tonsils to acute rheumatism during childhood, *Am Jr Dis Child*, 1929, xxxvii, 559-564
 - ⁵⁰KATZ, B Tonsillectomy in relation to the recurrence of rheumatic manifestations, *Med Jr and Record*, 1931, cxviii, 185-187
 - ⁵¹BURNETT, C T Occult rheumatism, *Colorado Med*, 1928, xxv, 212-214
 - ⁵²PAUL, J R Pleural and pulmonary lesions in rheumatic fever, *Med*, 1928, vii, 383-410
 - ⁵³COHN, A E Heart disease from the point of view of the public health, *Am Heart Jr*, 1927, ii, 275-301
 - ⁵⁴CHRISTIAN, H A Chronic nonvalvular cardiac disease or chronic myocardial insufficiency and its therapeutic management, *Ann Int Med*, 1931, v, 95-99
 - ⁵⁵LEECH, C B Value of salicylates in the prevention of rheumatic manifestations, *Jr Am Med Assoc*, 1930, xcv, 932-934
 - ⁵⁶HAGEBUSH, O E, and KINSELLA, R A Effect of sodium salicylate on intradermal reactions of rabbits, *Proc Soc Exper Biol and Med*, 1930, xxvii, 922-924
 - ⁵⁷SMALL, J C Streptococci in relation to rheumatic disease, *Med Clin North America*, 1930, xiii, 857-868
 - ⁵⁸SIMON, F A Clinical comparison of acetyl-salicylic acid analgesia with and without magnesium oxide, *Jr Lab and Clin Med*, 1931, xvi, 1064-1066
 - ⁵⁹SCHWARTZ, S P, and SCHWEDEL, J B Digitalis studies on children in heart disease—II The effect of digitalis on the sinus rate of children in rheumatic fever and chronic valvular heart disease, *Am Jr Dis Child*, 1930, xxxix, 298-315
 - SCHWARTZ, S P III Auricular fibrillation in children with an early toxic digitalis manifestation, *Am Jr Dis Child*, 1930, xxxix, 549-559
 - ⁶⁰LEVY, R L, and GOLDEN, R Treatment of rheumatic carditis by roentgen irradiation of the heart, *Am Heart Jr*, 1928, iv, 127-144
 - ⁶¹NEUHOF, S The heart, 1923, Blakiston, Philadelphia
 - ⁶²DILLON, J F Rheumatic carditis, autopsy, *West Med Chir J*, 1850-51, i, 1-6
 - ⁶³GRAMSHAW, H Case of rheumatic carditis, *Med Times Gaz*, 1853, vi, 55
 - ⁶⁴MORSE, J L The prognosis of acute endocarditis in childhood, *Am Jr Dis Child*, 1931, xlii, 735
- The following articles have been consulted but are not specifically referred to in the text
- REINHART, A S Evolution of clinical concept of rheumatic fever, *New England Jr Med*, 1931, cciv, 1194-1199
 - SCHMITZ, H W, and SHERMAN, E Urobilinuria in children with rheumatic heart disease, *Am Jr Med Sci*, 1931, clxxx, 392-398
 - GERSTLEY, J R Rheumatic fever, subacute bacterial endocarditis and focal infection, *Med Clin North America*, 1931, xiv, 1221-1227
 - HELMHOLZ, H F Rheumatic fever in childhood, *Minnesota Med*, 1931, xiv, 5-7
 - HOFFMAN, M H Rheumatic carditis, *Minnesota Med*, 1931, xiv, 8-11
 - GARDNER, E L The protean patho-

- logical manifestations of rheumatic fever, *Minnesota Med*, 1931, xiv, 12-13.
- OERTING, H The nonarticular forms of rheumatic fever, *Minnesota Med*, 1931, xiv, 14-15
- FONI, A. N The relation between acute rheumatic fever and subacute bacterial endocarditis, *Med Jr and Record*, 1931, cxxiii, 126-129
- DUNNING, H S Paroxysmal cardiac pain in a patient with rheumatic heart disease, *Am Heart Jr*, 1931, vi, 565-567
- WOOD, F C, and ELIASON, E L Rheumatic peritonitis, *Am Jr Med Sci*, 1931, clxxi, 482-494
- THAYER, W S Observations on rheumatic pancarditis and infective endocarditis, *Ann Int Med*, 1931, v 247-255
- STRANG, J M, and SEMSROTH, K. Streptococcic septicemia with vascular lesions, *Arch Int Med*, 1931, xlvii, 583-592
- SUTTON, L., and WYCKOFF, J Digitalis, its value in the treatment of children with rheumatic heart disease, *Am Jr Dis Child*, 1931, xli, 801-815
- FRASER, A D The Aschoff nodule in rheumatic pneumonia, *Lancet*, 1930, i, 70-72
- SCHWARTZ, S P, and SHELLING, D Acquired rheumatic pulmonic stenosis and insufficiency, *Am Heart Jr*, 1931, vi, 568-574
- WIGGLRS, C J The principles and practice of electrocardiography, 1929, C V Mosby and Co, St Louis

Early Manifestations of Rheumatic Infections in Young Children*

By C C McLEAN, M D , F A C P , *Birmingham, Alabama*

THE early manifestations of rheumatic infections in children are characterized by an insidious onset. Such children are pale, easily fatigued, have poor appetites and are not gaining in weight as they should. Many complain of slight pains in the legs, feet or joints. There is often stiffness of limbs or neck. Digestive disturbances with paroxysmal abdominal pains are common. There is a change in disposition. The children become irritable, nervous, peevish and are easily frightened. Often there is a failure in mental concentration and they begin to drop objects and at times have difficulty in writing. There may be slight muscle twitching. Examination shows an anemic child who is irritable, nervous, excitable, high strung and usually underweight.

The second heart sound is accentuated, with a soft blowing systolic murmur heard over the apex, that may or may not be transmitted. When the murmur is heard in a patient in whom it did not previously exist and is known to remain constant for at least

a month, during which time the patient is free of temperature and acute infections, the diagnosis of a rheumatic infection is almost certain. Often no murmur is heard, but the heart action is rapid and the apex impulse exaggerated.

In the registration area¹ the death rate from organic heart disease has been increasing gradually for a long series of years. In 1910 in New York City,² the death rate due to heart disease was 175 per 100,000 population. In 1925 the rate was 266 per 100,000 population, showing an increase of 34 per cent. Drolet tells us that heart disease in New York is now responsible for more than one-fifth of the total deaths.

Wyckoff and Lingg³ analyzed 1000 cases of heart disease and found 25 per cent to be rheumatic, 40 per cent arteriosclerotic, 10 per cent syphilitic and 10 per cent of unknown etiology.

Munly⁴ analyzed 1300 cases of heart disease and found that the rheumatic type comprised 35 per cent of the total, arteriosclerotic, 33 per cent, syphilitic, 8.5 per cent, unknown, 20 per cent. Of the unknown group it is believed by most investigators, that they are chiefly of rheumatic origin, the

*Read before the Chattahoochee Valley Medical and Surgical Association, Radium Springs, Ga., July 14, 1931. Received for publication, October 22, 1931.

heart condition being the only manifestation of the rheumatic infection

In the registration area in the United States in 1928 in children between the ages of 5 and 15 years, rheumatic infections and their complications caused as many deaths as any disease, with the exception of the various types of pneumonia.⁵ The American Heart Association stated, "if present conditions continue, one in every five of population living at age 10 will die of heart disease."

Feer⁶ stated that 80 or 90 per cent of all cases of rheumatic infection will have a certain degree of heart involvement. Riesman and Small⁷ stated that cardiac involvement is part and parcel of the rheumatic process and is no more a complication or sequella than is the involvement of the shoulder joint a day or more after that of the knee. Coombs⁸ states, "The heart may be damaged without manifestations of the infection. Every child that has rheumatic polyarthritis, which can be recognized as such, may be assumed to have an affected heart." Still⁹ in his excellent book wrote, "There is no more pitiful sight than seeing a child dying from rheumatic carditis. It is hoped that by recognition of these cases in the early stage, that some of the terrible results can be prevented."

It has been found that heart disease reduces the span of life by practically one-half. It is a well known fact that an established heart lesion in the early stages can often become stationary by the cooperation of the patient who receives the proper medical supervision and instruction. Rheumatic infections are thought to be responsible for approximately 10 per cent of

the total cardiac deaths, the majority of the patients contracting the heart condition in early childhood.

From the above observations and statistics it seems logical that the way to reduce the mortality from rheumatic heart disease is to prevent its development in every way possible. If every child with early manifestations of rheumatic infection was considered a potential cardiac patient and managed accordingly, and the parents and patient educated to the danger of the condition, the mortality from rheumatic disease would be reduced in both childhood and adult life.

The following is a report of clinical observations in 258 patients, observed in private practice, with early manifestations of rheumatic infections. Of this number 132 were boys and 126 girls. One hundred eighteen of the patients were reported in 1929.¹⁰ The largest number of cases were seen in the late winter and early spring. Fifty-eight per cent of the patients were seen in the months of January, February, March, and April. The largest number of cases were seen in March.

The following are the ages when the children were first seen with manifestations of the infection: 75 between 2 and 5 years, 86 between 5 and 7, and 97 after the age of 7 years.

Every patient had all or some of the following symptoms. They were pale, high strung, nervous, irritable children, easily fatigued, with poor appetites, who were either losing weight or not gaining as they should. Two hundred three, or 80 per cent, gave histories of repeated attacks of tonsillitis. Two hundred two, or 78 per cent, had soft blowing systolic heart murmurs. No child is included in this

series as having a heart murmur except those patients in whom the murmur was known to exist and remain constant for at least one month, during which time the child was free of temperature and acute infections.

One hundred seventy-five, or 68 per cent, gave histories of pains in the extremities or stiffness of the joints. One hundred fifty-four, or 60 per cent, were 7 per cent or more underweight for height. Seventy-one, or 28 per cent, gave histories of digestive disturbances characterized by paroxysmal abdominal pains. In 70, or 27 per cent, there were signs and symptoms of a mild chorea. Of this number 38 were girls and 32 boys. Many gave histories of night terrors, enuresis and tachycardia.

TABLE 1
The Number of Children and the Percentage Underweight for Age and Height

Percentage Underweight	For Age No. Patients	For Height No. Patients
1-6	63	60
7-10	36	50
11-14	33	50
15-20	25	39
21-25	7	15
Over 25	4	0
Total	168	214

FOCI OF INFECTION

In young children apparently the foci of infection were largely in the tonsils, nasopharynx and teeth. Foci of infection were thought to be located as follows:

- 126 cases, tonsils and adenoids,
- 49 cases, teeth or both teeth and tonsils,
- 21 cases, chronic nasopharyngitis or paranasal sinusitis,
- 62 cases, undetermined

One hundred twenty-six, or 50 per cent, of the total number of children were known to have manifestations

of rheumatic infections before the tonsils and adenoids were removed. Of this number 114, or 90 per cent, developed systolic heart murmurs. There were signs and symptoms of a mild chorea in 11 per cent. In 29 cases in which the teeth alone were thought to be the foci of infection, heart murmurs were present in 38 per cent and signs of chorea in 62 per cent. In 20 cases in which both the teeth and tonsils were apparently the foci of infection, heart murmurs were present in 75 per cent, signs of chorea in 55 per cent. Twenty-one cases in which the nasopharynx and paranasal sinuses were thought to be the foci of infection, were either irregular patients or cases having the tonsils and adenoids removed before being seen. In the majority there were histories of repeated attacks of tonsillitis.

Of the 62 cases in which the foci of infection were undetermined, heart murmurs were present in 79 per cent, signs of chorea in 30 per cent. In the majority of these cases the tonsils and adenoids were removed before the patient was seen. In many, before the operation, there was a definite history of rheumatic infections. Approximately 75 per cent gave histories of repeated attacks of tonsillitis. Otitis media was a very common occurrence. Many of the children had signs and symptoms suggestive of a paranasal sinusitis.

Ninety-one patients, 52 boys and 39 girls, developed heart murmurs while under observation. In 54, or 59 per cent, of the cases the murmur was first heard between the ages of 3 and 6 years. A diagnosis of chronically diseased tonsils and adenoids was

TABLE 2
Summary of Clinical Observations in 258 Patients with Early Manifestations of Rheumatic Infections, with Grouping According to the Apparent Foci of Infection

Foci of Infection	No Patients	Heart Murmurs		Pains in Ext or Stiffness of Joints		Pains in Abdomen		Sympt and Signs of Chorea	
		No	Pts %	No	Pts %	No	Pts %	No	Pts %
Tons ad Nasopharynx	126	114	90	84	67	40	32	14	11
Teeth, tonsils	20	15	75	15	75	4	20	11	55
Ad nasophar Teeth	29	11	38	19	66	5	17	18	62
Nasophar paranas sinus, etc	21	13	62	18	86	7	33	8	38
Undetermined	62	49	79	39	63	15	24	19	31
Total	258	202	78	175	68	71	28	70	27

made in 93 per cent of the cases. Eighty-five per cent were seen one or more times with attacks of acute follicular tonsillitis. From 1 to 2 years before the murmur was heard, 39 per cent of the children were 7 per cent or more underweight for height. At the time of murmur the number had increased to 49 per cent. In 69, or 76 per cent, of the children the murmur was heard before the tonsils and adenoids were removed. No murmur was heard in 22, or 24 per cent, of the cases until after the operation. In 6 of these 22 patients, a diagnosis of a rheumatic infection had been made before the removal of the tonsils and adenoids. Eight cases were seen at irregular intervals and it is possible that the children had the heart murmur before the operation. At the time of murmur, 30 patients gave histories of pains in the extremities. Six were treated for pains in legs before murmur was heard. Ten cases, at the time of the murmur with negative histories, developed symptoms later.

Thirty-three, or 36 per cent, of the children had digestive disturbances characterized by paroxysmal abdomi-

nal pains, the majority were of such severity that the patients were brought to the office for treatment.

CHOREA

At the time murmur was heard, 3 of the children had signs and symptoms of a mild chorea. From 1 to 4 years after the diagnosis of a rheumatic infection, 6 patients developed symptoms of a mild chorea. In 4 of the 6 cases the teeth were apparently the new foci of infection.

Twenty-four children developed signs and symptoms of a more or less chronic paranasal sinusitis after the removal of the tonsils and adenoids. In these cases there was little improvement in either their physical condition or the rheumatic infection.

LABORATORY FINDINGS

At the time the children were first seen with manifestations of rheumatic infections, white blood counts were made in 167 patients. The lowest count was 4,000, highest, 31,000, average, 11,101. Fifty-eight per cent of the counts were between 9,000 and 12,000. Differential blood counts made in 175 patients showed the

neutrophile percentage above average for the age in 61 per cent of the cases. In 33, or 30 per cent, the neutrophiles were from 15 to 35 per cent above the normal average for patients of the same age.¹¹

Hemoglobin estimations were made in 177 patients (Dare and Talquist). The lowest reading was 40 per cent, the highest, 90 per cent, average, 66.7 per cent. One hundred fifteen, or 65 per cent, of the readings were between 40 and 70 per cent. One hundred sixty-seven, or 94 per cent, were between 50 and 80 per cent.

TABLE 3

Hemoglobin Percent	No. Cases
40-50	5
50-60	31
60-70	57
70-80	53
80-90	31
Total	177

Red blood counts were made in 42 patients. There were 18, or 43 per cent, of the blood counts between 3 and 4 million, 52 per cent between 4 and 5 million, and 5 per cent over 5 million.

Our records show urinalysis in 222 of the patients. In 23 cases albumin was present, casts were found in 4, only 3 of the children proved to have a nephritis. One child was found to have a pyelitis.

Wassermann tests made in 139 children were negative.

Tuberculin tests, intracutaneous and Craig's modification of the Von Pirquet tuberculin test, were done in 198 of the patients. Fifteen, or 7 per cent, gave a positive reaction.

COMMENT

The medical profession considers tuberculosis as either active or inactive and the patient is treated accordingly. The same should be true of rheumatic infections.

Rheumatic fever and other manifestations of the infections are characterized by repeated recurrent attacks. We have often seen cases free of symptoms for months, but when the resistance of the child was lowered from any of the following causes, (1) overwork, (2) fatigue, (3) too much excitement, (4) acute infections, (5) development of new foci of infection, or (6) re-infection of old foci, new manifestations of the rheumatic infection developed.

Many of the patients seen with rheumatic carditis in both young and late adult life, had evidently contracted the disease in early childhood before their tonsils and adenoids were removed. In cases seen with manifestations of rheumatic infection before the tonsils and adenoids were removed, a large percentage developed systolic heart murmurs and a small percentage had signs and symptoms of chorea. In the cases in which the teeth were apparently the foci of infection, the nervous symptoms were more pronounced, usually the heart action was rapid and the apex impulse exaggerated. There were fewer systolic heart murmurs and a decided increase in the number of children with signs and symptoms of mild chorea.

In 9 children heart murmurs were apparently the only manifestations of the rheumatic infection. Six cases between the ages of 2 and 4 years had been seen repeatedly with attacks of acute follicular tonsillitis. Loud, blow-

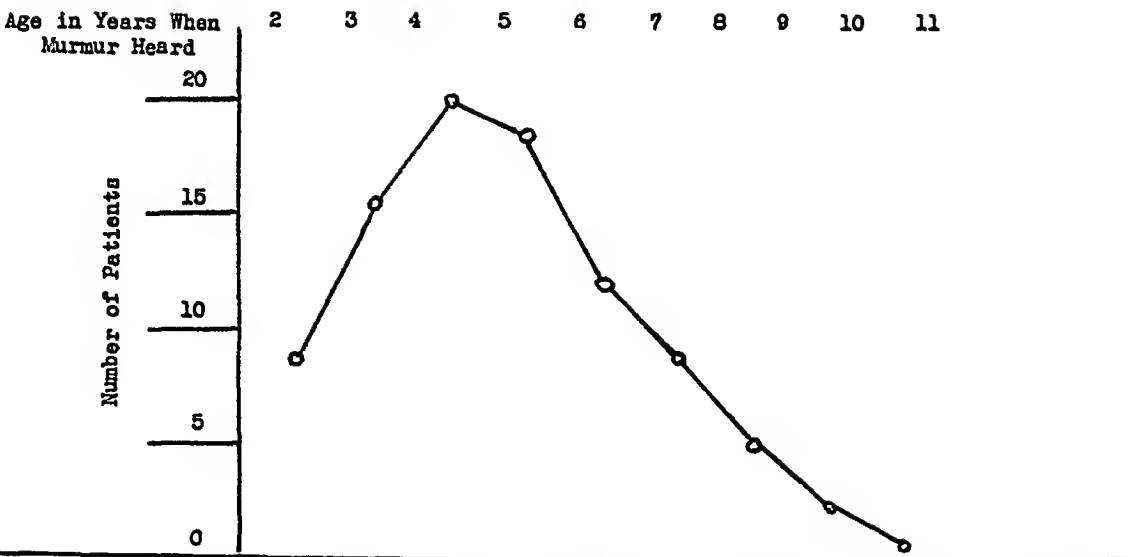


FIG 1 The age curve of 91 patients with heart murmurs who developed the condition while under observation

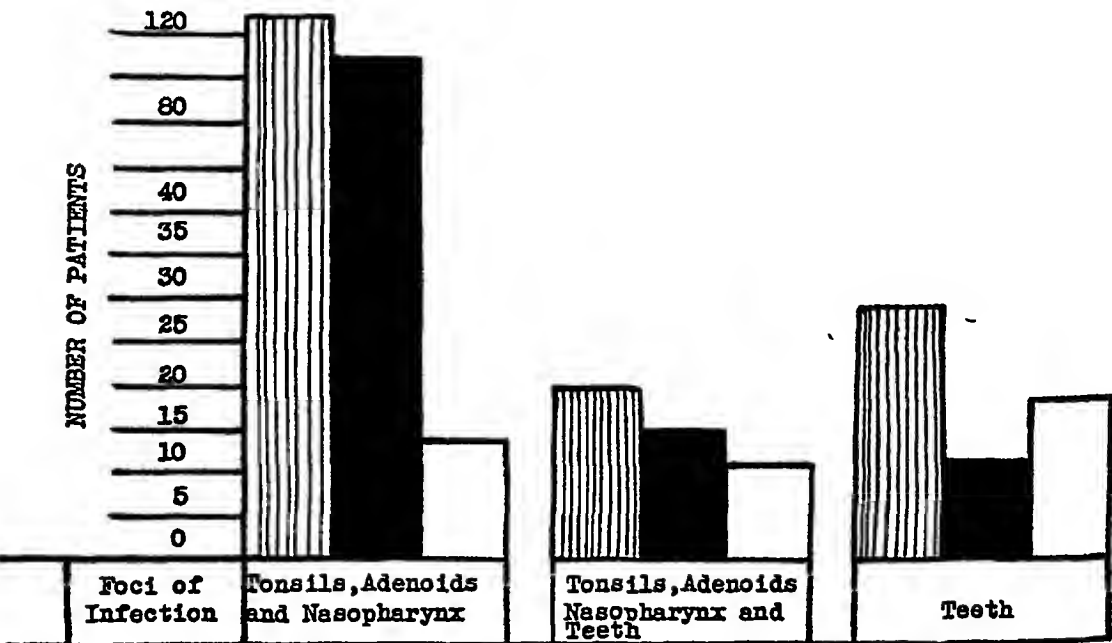


FIG 2 The incidence of heart murmurs and signs and symptoms of chorea in patients in whom the tonsils, adenoids, nasopharynx and teeth were apparently the foci of infection
Shaded column—number of patients
Black column—number of patients with heart murmurs
White column—number of patients with signs and symptoms of chorea

ing systolic heart murmurs were discovered in each case between attacks of tonsillitis. The tonsils and adenoids were removed and the murmurs have remained constant for a period of from 2 to 5 years.

Three children who did not look acutely ill or toxic, ran high and widely fluctuating temperatures for several weeks, with negative physical and laboratory findings. Later, in each case, loud blowing systolic heart murmurs developed.

In the cases reported, apparently there was little or no hypertrophy of the heart. In x-ray study, the teleroentgenogram measurements in the majority of cases taken were within the normal limits. In fluoroscopic examinations, in a few cases there was a definite prominence in the region of left auricle making the left border of the heart almost a straight line.

During the period of observation, in the majority of the instances in which the cooperation of the parents and children was obtained, the heart murmurs have remained constant, with little or no change. In a certain number of cases the heart condition has progressively grown worse. In a small percentage of cases the murmurs have apparently disappeared.

Many children made little or no improvement after the tonsils and adenoids were removed. This was especially true in cases known to have had chronically diseased tonsils and adenoids. The children who did not respond to the operation, almost invariably developed signs and symptoms suggestive of a paranasal sinusitis. The most characteristic symptoms in the order named, follow (1) The tongue is coated and breath often

bad, (2) the uvula is enlarged, swollen and edematous, stretching into a narrow thread like projection clinging to the back of the throat, (3) when the patient is made to gag and contract the muscles of the nasopharynx, a muco-purulent discharge is seen, (4) intermittent cough, paroxysmal in type of several weeks or months duration, the cough being worse at night, (5) the retropharyngeal glands, especially behind the posterior tonsillar pillar are usually enlarged.

Due to the severity of paroxysmal abdominal pains caused by a demonstrable spasmodic contraction of the intestines in 24 children between the ages of 3 and 7 years, a diagnosis of enterospasm was made. The patients were given atropine. Sixteen of the cases at the time of diagnosis had symptoms or signs of a rheumatic infection. Three of the patients later developed manifestations of the infection. The records show a diagnosis of chronically diseased tonsils and adenoids in 16 of the 24 cases.

So many of the patients were seen with otitis media and asthmatic bronchitis that the records were investigated to see if children with manifestations of rheumatic infections had been more susceptible to respiratory infections than children with no manifestations. The number of respiratory infections seen in 84 patients over an exact period of 5 years from the date of birth, is tabulated in Table 4. The infections are listed as mild and severe. The mild infections include ambulatory cases with little or no temperature, comprised principally of mild upper respiratory types of infections. The severe infections include bed cases, acutely ill with high tempera-

ture, comprised principally of so-called influenza with its various complications, acute bronchitis, acute follicular tonsillitis, etc

from 11 to 12 hours sleep They are dressed warmly and not allowed out of the house on cold, damp days They do much better in warm, dry climates

TABLE 4
The Number of Respiratory Infections Seen in 84 Patients for an Exact Period of Five Years from the Date of Birth

	No of Pts	No of Resp Inf			Aver No Resp Inf per Pt		
		Mild	Severe	Total	Mild	Severe	Total
Pts with mans of Rheumatic inf	23	81	139	220	3 52	6 04	9 56
Pts without mans of rheumatic inf	61	232	376	608	3 8	6 16	9 96

Twenty-three of the 84 patients had manifestations of a rheumatic infection, 61 patients had no manifestations of a rheumatic infection The average number of respiratory infections per patient for an exact period of 5 years from the date of birth in the rheumatic cases, was 9 56; non-rheumatic cases, 9 96 The rheumatic cases had 3 52 mild and 6 03 severe infections The non-rheumatic cases had 3 8 mild and 6 16 severe infections

MANAGEMENT

Every effort is made to keep the child's attention from the heart The patients are never told they have a cardiac condition In the management of children it is essential to obtain the confidence and cooperation of the parents by educating them to the danger of the condition

Every child with manifestations of an early rheumatic infection is given the benefit of the doubt and treated accordingly What is thought to be the focus of infection is found and removed when practical Satisfactory results are often obtained by local treatment of the focus Rest in bed and forced feeding are very important The children should have

than in cold, wet ones The danger of acute infections should be explained to the parents and the children protected in every way possible

Our routine when the patient is first seen with early manifestations of rheumatic infections, is to keep the case in bed with the exception of four hours each day, for a period of two to six weeks During the four hours a day out of bed, the child is usually allowed to do as he pleases, no restrictions being made if possible They are given a well balanced, six meal diet, with especial emphasis on liver, spinach, prunes, whole wheat breads, and cereals They are also given malt, iron, and cod liver oil

One hundred forty-four patients given rest treatment and forced feeding for 518 weeks gained 486 pounds The average number of weeks of forced feeding and rest treatment per patient was 3 5 weeks The average number of pounds gained per patient was 3 4 pounds There was an average gain per patient of 15 ounces per week

The strain of the long hours of school routine is too great for the average child with a well developed

TABLE 5
One Hundred Forty-Four Patients Given Rest Treatment and Forced Feeding for
518 Weeks, Gained 486 Pounds

	No of Weeks									Aver No of Wks per Pt	Aver No lbs gained per Pt	Aver gain in Oz per Wk per Pt
Rest treatment and forced feeding	1	2	3	4	5	6	7	8	9	35	34	15
Number of pts	9	42	29	28	12	13	1	9	1			

rheumatic infection. It was found necessary to remove many children from school two or three times each year and give rest treatment and forced feeding. The physical condition of certain children was such that they could attend school but half a day.

SUMMARY

1 Organic heart disease causes more deaths in the United States than any other condition. Of the total cardiac deaths, approximately 40 per cent are thought to be of rheumatic origin. In a majority of cases the disease is contracted early in childhood.

2 Of 258 patients with early manifestations of rheumatic infections, 126 were girls and 132 boys. One-third of the total number of cases were first seen with manifestations of the infection between the ages of 5 and 7 years.

3 Of the children, 203, or 80 per cent, gave histories of repeated attacks of tonsillitis.

4 Two hundred two, or 78 per cent, had soft blowing systolic heart murmurs.

5 One hundred seventy-five, or 68 per cent, had pains in the legs, joints, or stiffness of the limbs.

6 Seventy-one, or 28 per cent,

gave histories of digestive disturbances, characterized by paroxysmal abdominal pains.

7 In 70, or 27 per cent, there were signs and symptoms of a mild chorea. Of this number 38 were girls and 32 boys.

8 Two hundred forty, or 82 per cent, were underweight for their height. For the age, 168, or 63 per cent, were underweight.

9 Ninety-one patients, 52 boys and 39 girls, developed heart murmurs while under observation. In 58 per cent of the children the murmurs were first heard between the ages of 3 and 6 years.

10 In 126 patients, 50 per cent of the total number, the tonsils and adenoids were thought to be the foci of infection, 114, or 90 per cent, developed heart murmurs, 14, or 11 per cent, had signs of chorea.

11 Of 49 cases in which the teeth were apparently the only foci, or one of the foci of infection, 26, or 53 per cent, had heart murmurs, 29, or 59 per cent, had signs of chorea.

12 In 177 patients the average hemoglobin reading was 67 per cent.

13 The incidence and severity of respiratory infections, during the first five years of life, were apparently no

greater in the rheumatic than in the non-rheumatic children

14 The patients in whom the results from tonsillectomy and adenoidectomy were disappointing, almost invariably developed signs and symptoms suggestive of a paranasal sinusitis. This was especially true in the cases known to have had chronically diseased tonsils and adenoids

15 During the period of observation in the majority of instances in which the cooperation of the parents and children were obtained, the heart murmurs have remained constant with

little or no change. In a certain number of cases the heart condition has progressively grown worse. In a small per cent of cases the murmur has apparently disappeared

16 One hundred forty-four patients given rest treatment and forced feeding for a period of 518 weeks, gained 486 pounds, an average gain per patient of 15 ounces a week

CONCLUSIONS

Every child with early manifestations of rheumatic infections is a potential cardiac patient and should be managed accordingly

REFERENCES

- ¹Heart disease and its prevention, Am Heart Assoc, 1928, Series No 4, 4-6
- ²DROLET, G J Heart disease the outstanding health problem New York Tuberculosis and Health Assoc, 1926, Bull 7, 18-22
- ³WYCKOFF, J, and LINGG, C Statistical studies bearing on problems in the classification of heart disease 2 Etiology in organic heart disease, Am Heart Jr 1926, 1, 446-448
- ⁴MUNLY, WM C Problems in the prevention and relief of heart disease, Am Jr Pub Health, 1928, xviii, 1098-1100
- ⁵STERLING, BLANCHE Statistics in registration area in United States, 1928 Congressional Record, U S Gov't Printing Office, Washington, 1931 (60690-7403), 44
- ⁶FEER, E Pediatrics, First Eng ed, 1922, 707
- ⁷RIESMAN, D, and SMALL, J C Rheumatic fever, clinical manifestations, etiology and treatment, Ann of Int. Med, 1929, 11, 637-639
- ⁸COOMBS, CAREY F The diagnosis and treatment of rheumatic heart disease in its early stages, Brit Med Jr, 1930, 1, 227-229
- ⁹STILL, C F Common disorders and diseases of childhood, Fifth ed, 1927, 576-78
- ¹⁰MCLEAN, C C Early rheumatic infections of childhood, Arch of Ped, 1929, xli, 657-59
- ¹¹SCHLOSS, O M The normal percentage of the different variations of leukocytes in infants and children, Arch Int Med, 1910, vi, 638-40

Causes, Classification and Differential Diagnosis of Anemias*†

Based on the Detailed Examination of Over Two Hundred Patients and a Study of the Literature

By EDWIN F OSGOOD, M D, F A C P, and HOWARD D HASKINS, M D,
Portland, Oregon

THIS is a presentation of the views formulated during a seven years' study of the clinical and laboratory phases of anemias and the literature pertaining thereto. Details of the subjects chosen, technic used, and results of the color, volume and saturation index studies are given elsewhere.¹

It has long been customary to divide anemias into two groups. Under the term primary anemia were included cases of pernicious anemia and, sometimes, chlorosis, and under the name secondary anemia, all others. These names were given as the cause was supposed to be unknown in primary anemias and known in secondary anemias. Since this classification is illogical in that it groups unrelated conditions together and tends to discourage thinking, it should be discarded.

*From the Departments of Medicine and Biochemistry, University of Oregon Medical School, Portland, Oregon

†Received for publication, July 30, 1931

Acknowledgment is due to P. Blakiston's Son & Co., Inc., 1012 Walnut St., Philadelphia, for permission to include in this article excerpts from the Textbook of Laboratory Diagnosis by Edwin E. Osgood and Howard D. Haskins.

FUNDAMENTAL CAUSES OF ANEMIA

Obviously there are only three fundamental causes of anemia.

1 Deficient production of red cells, or of hemoglobin, or of both, either due to lack of materials (chlorotic type) or to lack of active blood-forming tissue (aplastic or myelophthisic type)

2 Abnormally rapid destruction of red cells or hemoglobin, or both, in the body (the hemolytic type, internal hemorrhage, etc., are included in this group)

3 Hemorrhage or loss of red cells and hemoglobin from the body (anemia of blood loss)

As all clinical anemias result from various combinations of these factors, they deserve special study.

1 *Deficient production of red cells*
This is the group about which we know least.

(a) Deficient supply of erythrocyte-building material. Iron, certain other metals, and probably other, as yet unidentified, substances are necessary for the formation of hemoglobin.² Hence, it is probable that deficiency in these substances leads to a low color index and more severe deficiency leads to a low saturation index. Deficiency

in stroma-building materials, the nature and occurrence of which is not known, might lead to a low volume index, or the low volume index might be secondary to a decreased supply of hemoglobin, but this is as yet pure hypothesis. The most effective therapy would be to supply the deficient substances. Chlorosis is the type anemia of this group.

(b) Aplasia of erythropoietic tissue. Here we expect absence of evidences of red cell regeneration. Therefore, reticulocytes, polychromatophilic cells, and nucleated red cells should be absent from the blood stream, and, as the other myelogenous elements are seldom³ spared*, one would expect, also, leucopenia, affecting chiefly the myeloid cells (granulocytes), and thrombopenia with the associated prolonged bleeding time, delayed clot retraction and hemorrhagic tendency. Certain poisons, especially benzol,⁴ are known to produce this syndrome, and it is probable that also some bacterial toxins can produce it. It may be pro-

*The extremely rare condition of progressive postinfectious erythrophthisis in which only erythropoiesis is disturbed is the third member of the group of specific bone marrow dysfunctions, agranulocytosis and thrombopenic purpura (some types) are the other two. In aplastic anemia, all three functions are impaired.

It seems probable that these four conditions may be merely different responses of different individuals to different quantities of the same toxin. For example, it is possible experimentally to produce pictures closely simulating any one of these syndromes by varying the doses and the duration of exposure to benzol. A further point suggesting that this is true, is that cases occur showing clinical features intermediate between any two of these conditions.

duced by excessive exposure of blood forming tissue to roentgen rays or radioactive substances⁵ and in some cases is due to almost complete destruction of marrow by invasion of other tissue (osteosclerotic anemia and rare instances of malignancy). A few cases occur for which the cause has not been determined and they are grouped under the term idiopathic aplastic anemia. The only therapy that can be expected to be effective in the aplastic cases is removal of the cause and restoration of bone marrow function, although blood transfusion may be of temporary benefit. It is theoretically possible that this deficient function might be due to absence of a normal stimulus.

The only compensatory mechanism available to the body to combat decreased formation of red cells and hemoglobin is to prolong the life of those formed (decreased rate of destruction). The evidences of this are decrease in the icterus index below 25, decrease in urobilinogen in the stools, and a greater tendency for it to be absent from the urine. It is possible, but by no means certain, that poikilocytosis and microcytosis are evidences of abnormal length of life in erythrocytes. As the same changes in the aplastic type affect the granulocytes, it is to be expected that they also will show evidence of decreased rate of destruction (increased proportion of segmented forms with five or more nuclear subdivisions).

(c) Destruction of bone marrow (myelophthisic anemia). This is usually due to invasion by other tissue (leukemias, myeloma, malignancies involving the marrow, osteosclerosis, etc.) but may be due to extensive

osteomyelitis. Although there is often an absolute deficiency in marrow, there is a tendency for that near the lesion to be irritated to abnormal activity (evidenced by unusually immature red and white cells in the blood stream) and for uninvolved marrow to be capable of compensatory hyperactivity. Attempts at compensation by decreased blood destruction may also occur. Hence, the characteristic findings are those of the causative disease (leukemia, etc.) plus the presence of immature erythrocytes (reticulocytes, polychromatophilia, nucleated red cells including megaloblasts) and old red cells (poikilocytes, great anisocytosis), immature granulocytes (even back to the myeloblast with a tendency for eosinophils and basophils to increase as well as neutrophils), and old leukocytes (cells with five or more segments), thus giving rise to a very bizarre blood picture. The color, volume, and saturation indices are variable but most often within normal limits. A low icterus index and decreased urobilinogen excretion is present when decreased red cell destruction occurs. Removal of the cause is the only therapy likely to be of benefit.

2 *Increased Rate of Red Cell Destruction within the Body* This may be due to extravasation of blood (hemorrhage into body cavities or tissues, hemorrhagic infarcts, etc.), to hemolysis (hemolytic poisons, some bacterial toxins, or hypotonicity of the medium, as after distilled water injections, etc.), to destruction of red cells in the blood stream (malaria), to hyperactivity of the normal blood cell destroying mechanisms, to the production by the bone marrow of red cells with decreased resistance to the factors

normally tending to destroy them, or to some abnormality in another organ (spleen?) affecting the red cells in such a way as to decrease their resistance.

The evidences of increased rate of red cells destruction will be common to all. These are an increase in the blood bilirubin (increased icterus index with negative direct van den Bergh reaction and no tendency to bilirubinuria), increase in urobilinogen in the stools and a tendency for it to appear in the urine in abnormal amounts.

If no other factor than increased blood destruction plays a part, there will be evidence of rapid regeneration of cells, because the remnants of the destroyed corpuscles and hemoglobin within the body insure the continuous presence of an excess of erythrocyte and hemoglobin-forming materials*. Hence, one would expect to find in a purely internal blood destruction anemia, an increase in young erythrocytes, other evidences of increased bone marrow activity (neutrophilia with increased proportion of immature forms, and thrombocytosis), and red cells of normal size and hemoglobin content (normal color, volume and saturation indices).

Rapid regeneration of cells by the bone marrow is the compensatory mechanism in this group, and in uncomplicated cases, removal of the cause is the only therapeutic measure indicated, for the body already contains an excess supply of erythrocyte-forming materials, from the destroyed cells.

*It is theoretically possible that interference with the transport mechanism would prevent these from being available at the point where they are needed.

It is further obvious that if regeneration keeps pace with cell destruction, a cause for anemia of this type can exist without the production of an actual anemia, but the evidences of rapid erythrocyte destruction and of rapid erythrocyte regeneration will, nevertheless, be present

3 *Blood Loss from the Body* This includes all types of external hemorrhage, as well as hemorrhages from the air passages and gastrointestinal tract, in which blood leaves the body before destruction and reabsorption. Here, evidences of blood destruction will be lacking, but as long as adequate supplies of blood-forming materials are available, evidences of rapid red cell regeneration will be present. Therefore, the pictures for acute blood loss and chronic blood loss will be different

(a) *Acute blood loss* The deficiency in red cells and hemoglobin will not be apparent until increased plasma volume occurs. Compensation is by rapid regeneration from existing stores, so the evidences of increased bone marrow activity (reticulocytosis, polychromatophilia, nucleated red cells, neutrophilic leucocytosis, thrombocytosis) dominate the picture, and cells of normal size and hemoglobin content (normal color, volume and saturation indices) are formed as long as the supplies of stroma- and hemoglobin-building materials are not exhausted. Later, decreased color, volume and saturation indices may occur if the loss of blood was extreme, and decreased blood destruction (low icterus index, poikilocytosis) may occur as a compensatory factor; but these changes are never present in the first few days

(b) *Chronic blood loss* Here, the exhaustion of the hemoglobin-building (and probably also of stroma-building) material becomes the dominant factor, and this relative insufficiency gives rise to a picture almost identical with the absolute insufficiency (see 1 (a) above). Thus, evidences of compensatory decreased blood destruction and, to a less extent, of compensatory increased blood formation are both present, but the most characteristic change is a decrease in the color, volume and saturation indices, particularly the latter. Removal of the cause and administration of erythrocyte-forming substances are obviously both indicated. Here, too, it is possible for regeneration to keep pace with loss and, when the total blood volume and the normal rate of regeneration are considered, it is evident that the total quantity of blood lost per day must be very considerable (actual amount undetermined) to produce anemia, if no additional factors are present

DIFFERENTIAL DIAGNOSIS OF ANEMIAS

Unfortunately, clinical anemias are usually due to a combination of the above mentioned fundamental causes, and are in many instances too inadequately studied for one to be certain which of these factors plays the major rôle

In this study much material was accumulated to aid not only in the differential diagnosis of anemias but likewise in the determination of the fundamental factors responsible. It has seemed best to summarize these in tabular form since detailed presentation would exceed the space limits of

a journal article. Therefore, we have grouped, in the table, the chief diagnostic points in the more important clinical conditions in which the differential diagnosis of anemia arises. The figures* given in the table are based in part on our own experience and in part on a study of the literature. This literature is so extensive that space limitations prevent reference to all the articles consulted. Many of them will be found in the bibliographies given by Ordway and Gorham,⁶ but our files contain many articles on anemia and related subjects which they have not included.

The plan of the table is as follows. At the top are listed the data which it is most important to secure in differentiating anemias. Those tests followed by the letter A should be determined in every case in which anemia is considered. Those followed by B should be determined in almost every case. Those followed by C are less frequently of value and may be omitted except in the more puzzling cases, while those followed by D are still less frequently of aid in the differential diagnosis. Still other tests, such as cultures, platelet counts, and determinations of coagulation time, bleeding time and clot retraction time, will occasionally be desirable. The numbers in the first column are simply for reference. The second column

starts with normal men⁷ and women,⁸ the findings in whom serve as a basis for comparison. These are followed by twenty-eight conditions which must be considered when studying a patient thought to have anemia. This list could doubtless be extended, but includes the more important conditions. Note that the first sixteen are all characterized, as a rule, by color, volume and saturation indices within the normal range. The next group (17 to 20, inclusive) are sharply differentiated from the others by the high color and volume indices with normal saturation indices. The third group (21 to 23, inclusive) are characterized by a marked tendency toward a decrease in all three of these indices, and this is the only group in which a low saturation index occurs. The final group (24 to 28, inclusive) often have normal indices, but may show low color and volume indices. The numbers in the column headed "Relative Frequency" are in the approximate order of decreasing incidence, i. e., the conditions numbered 1 to 10 are very common, 11 to 20 are less common, and those above 21 are rare. In the remaining columns, an effort has been made to give, whenever possible, actual figures which will include approximately 95 per cent of the cases of each condition. The usual finding in a particular condition will, therefore, be intermediate between the extremes recorded.

In the column headed "Therapy," only the most specifically beneficial treatment is indicated and thus in the briefest possible form. Thus "liver" is meant to include not only liver itself, but liver extracts, desiccated stomach, and all nuclear material which has been shown^{11,12,13} to be effective in produc-

*An improved method of reticulocyte staining¹⁴ has been developed since the manuscript was submitted for publication. With this method the normal values are from 0.5 to 5.0 per cent, with an average of 1.5 per cent, and the average counts in the anemias will be about three times as great as would be inferred from the figures in the table.

ing a specific reticulocyte increase in patients with pernicious anemia. Similarly, "iron" refers not only to therapy with inorganic iron in large doses, but to therapy with all the known hemoglobin and stroma-building substances.² The large variety shown in this list of most important therapeutic procedures demonstrates incontestably the extreme importance of accurately determining the cause of any anemic condition. To merely prescribe a little iron and arsenic because the patient is thought to have a "secondary" anemia, in the present state of our knowledge, borders on criminal malpractice, for the anemia may be due to a readily removable cause (intestinal parasites, chronic lead poisoning, focal infection, bleeding hemorrhoids, etc.). To give "liver" therapy to such cases without an effort to determine and to remove the cause is equally undesirable. Accurate diagnosis is absolutely essential to adequate therapy.

The remainder of the table is largely self-explanatory, but a few points require comment. Obviously, the list of causes of acute and chronic hemorrhage and dietary deficiency anemias is very incomplete, while the individual subdivisions of the intestinal parasite, poisoning and infectious type anemias are not given. They should, however, readily suggest themselves to any well-trained physician. Note that the essential difference between acute internal and external hemorrhage is that, in the former, evidences of internal blood destruction appear within a few days, i.e., increase in the icterus index and in urobilinogen excretion. This may aid as well in differentiating cerebral hemorrhage from thrombosis or embolism, in differentiating hemor-

rhage from shock, ruptured ectopic pregnancy from most other acute conditions, and in detecting hemorrhagic infarcts, etc.

Note that in sickle cell anemia there are evidences both of rapid red cell destruction within the body and of rapid red cell regeneration, suggesting the possibility that the peculiarly shaped cells are especially susceptible to normal erythrocyte-destroying mechanisms.

Other myelophthisic anemias (malignant tumors involving the bone marrow, osteomyelitis, etc.) show findings similar to those in myelogenous leukemia with the exception that the white cell count in these conditions seldom exceeds 50,000 and the numbers of promyelocytes and myeloblasts tend to be less. Roentgenograms of the bones will usually decide the diagnosis. In each of these conditions, it is probable that a high color and volume index may occasionally occur, but the vast majority show normal indices.

Observe that the aplastic anemia picture is entirely different from that of pernicious anemia, and that there is no reason for confusing them, if the cases are properly studied. In aplastic anemia, the evidences of internal blood destruction are absent until internal hemorrhages occur.

Hemolytic icterus (familial or acquired) is the only group in which the fragility test is of prime importance. Note the almost constant decreased resistance of the red cells and increase in the reticulocyte count. Probably erythrocyte destruction and regeneration do not proceed at so rapid a rate in any other disease. It is, also, the only disease in which the volume index does not give the same informa-

tion as is derived from the determination of the average erythrocyte diameter. Hence, both determinations should be made whenever this disease is suspected.

Observe how sharply the pernicious group of anemias (17 to 20, with an occasional case of myelophthisic anemia, 7) are separated from all other types by the high color and volume indices. Since pernicious anemia itself is relatively common and all other members of the group are uncommon, such cases should be considered as pernicious anemia until proved otherwise. Note that a high color or volume index constitutes almost a specific indication for "liver" therapy.

It is important to keep in mind the fact that the pernicious anemia of pregnancy is rare, while other types of anemia are common in pregnancy. These have not been listed under a separate heading because it seems to the authors that most of the true anemias (disregarding the 10 to 20 per cent relative decrease in erythrocytes due to increased plasma volume in the last months) occurring in pregnancy can be placed in one of the other groups. It must not be forgotten that pregnant women are subject to most of the disease conditions to which non-pregnant women in a similar age group are susceptible and that they are hypersusceptible to some of them. It is probably true that due to the demands of the fetus for iron and other erythrocyte-building materials in the latter months of pregnancy, an anemia might develop on a dietary intake which would prove adequate for a non-pregnant woman, but the fact remains that this is a dietary deficiency anemia, giving rise to the same signs and symp-

toms and responding to the same therapy as in the non-pregnant woman. The tendency in pregnancy to pyelitis, nephritis, and other infections usually giving rise to anemia is well known.

Observe that most cases in the next group of conditions (21 to 23) are distinguished from all other types of anemia by the low saturation index. Low color and volume indices occur more commonly in these than in other conditions. Since, of these conditions, chronic hemorrhage alone is common, it seems justifiable to consider this as the most probable cause of an anemia in which the saturation index is below 0.85, until otherwise proved. Note that a low saturation index constitutes a specific indication for "iron" therapy and that administration of erythrocyte- and hemoglobin-building material may be expected to be of benefit in any anemia in which the color or volume index is low, while in other anemias such therapy is of very doubtful value.

The final group of anemias (24 to 28 inclusive) can be separated from group I only in the cases in which the color and volume indices are low. As a cause of anemia only the infection group is very common, for malignant tumors, in which ulceration (with secondary infection or hemorrhage) and bone metastases can be excluded, seldom cause anemia.

The most common cause of anemia is unquestionably infection. The mechanisms of the production of anemia in infection are probably chiefly bone marrow depression and internal blood destruction. In most infections, the evidence suggests that the former factor plays the predominating rôle. But in infections with organisms producing

a hemolytic toxin, the latter factor predominates. Unquestionably, the nature of the anemia varies with the type and virulence of the organism, with the location and extent of the infection, and with the condition of the hematopoietic system of the individual. It is probable that almost every infection, whether acute or chronic, has some anemia-producing tendency. This accounts for the fact that the so-called "normal figures" for hemoglobin and red cell count based on studies of hospital or dispensary patients who do not have the commonly recognized causes of anemia are consistently lower than figures based on studies of perfectly healthy persons.

Note that many of these conditions may co-exist with red cell counts and hemoglobin estimations within normal limits, that in myelogenous leukemia an actual erythrocytosis sometimes occurs, and that the lower limits of the counts and hemoglobin estimations are very variable in the different conditions. We have studied the blood of many pernicious anemia patients within a few hours of death and find the red cell counts usually between 400,000 and 800,000 and the hemoglobin between 1.5 and 3.0 gm per 100 cc. We feel certain that these figures represent the lower limits compatible with life. Hence, the figures of 143,000 reported by Quincke and of 138,000 reported by Naegeli were probably due to errors in technique.

The reader may make many other deductions from a study of the table. In individual cases, it must not be forgotten that two or more of these conditions may co-exist.

It is obvious that any theory of the etiology of pernicious anemia must ex-

plain the relationship to achlorhydria, the evidences of increased rate of red cell formation and red cell destruction, the large size of the circulating red cell, the occurrence of similar blood pictures in some cases of sprue and pregnancy, and the therapeutic value of liver, kidney, stomach, nucleated red cells and extracts of these tissues. The common factor in the effective therapeutic material would seem to be relative richness in nuclei. An hypothesis which might explain this syndrome is the following. In the nuclei of most mammalian organs and tissues there exists a substance which is necessary for the development of mature erythrocytes of normal size and resistance to the wear and tear of circulation and to the normal mechanisms for the destruction of red cells. The normal gastric secretion is capable of liberating this substance from skeletal muscle (meat) and other sources. In the common form of pernicious anemia, there is associated with the achlorhydria a deficiency of the digestive activity which liberates this effective substance. A deficient supply of this substance results in the formation of large cells by the bone marrow which are destroyed with exceptional readiness in the blood stream. This rapid destruction leads to the increased icterus index, to the increased excretion of urobilinogen in stools and urine, to the increased stores of iron in the liver and the spleen with resultant enlargement of these organs, and to the anemia. The anemia serves as a stimulus to more rapid red cell regeneration, giving rise to the tendency for nucleated, polychromatophilic and reticulated red cells to appear in the blood stream in increased numbers,

thus completing the hematologic picture of this disease. Organs rich in nuclei contain enough of this substance (probably not nucleoprotein or nucleic acid, but either a digestion product of these substances or something associated with them in the nucleus) in readily available form so that ingestion in large amounts gives an adequate supply even in the absence of the digestive substance. In sprue, the failure is probably in absorption (due to diarrhea) of the substance after liberation by digestion, while in the pernicious anemia of pregnancy, it is possible that there is a relatively insufficient intake of the substance to supply the needs of both the mother and the fetus.

SUMMARY

A table showing the results of the most important examinations in the different types of anemia is given, together with a discussion of the fundamental causes of anemias and the differential diagnosis of clinical anemias. A theory of the etiology of pernicious anemia is advanced.

CONCLUSIONS

1 The term "secondary anemia" should be discarded as it is not sufficiently descriptive and anemias formerly grouped together under this

term differ widely in etiology, symptomatology, blood findings, and in response to different types of therapy.

2 An accurate diagnosis of the etiology is essential to the proper treatment of anemias. To facilitate this differential diagnosis, a table is presented which gives the more important laboratory and clinical findings with the chief therapeutic indications in twenty-eight of the more important conditions which may cause or be confused with anemia.

3 A cause for anemia may exist without the development of actual anemia, since it is possible for blood regeneration to keep pace with blood destruction or with hemorrhage.

4 There are only three fundamental causes of anemia, i.e., deficient formation of red cells or hemoglobin, excessive destruction of red cells or hemoglobin within the body, and loss of red cells and hemoglobin from the body. These deserve more thorough study than they have previously received.

5 Clinical anemias should be studied with the object of determining what is the relative part played by each of these fundamental factors in any individual case. Criteria to use in this evaluation are indicated in this paper.

REFERENCES

- ¹OSGOOD, E. E., HASKINS, H. D., and TROMAN, F. E. The value of accurately determined color, volume and saturation indices in anemias, Jr. Lab and Clin Med. To be published.
- ²ROBSCHT-ROBBINS, F. S. The regeneration of hemoglobin and erythrocytes, *Physiol Rev*, 1929, ix, 666-709.
- ³BAAR, H. Progressive postinfektose Erythrophthuse, *Folia haemat*, 1927, xxxv, 111-115.
- ⁴SELLING, L. Benzol as a leucotoxin. Studies on the degeneration and regeneration of the blood and haematopoietic organs, *Johns Hopkins Hosp Rep*, 1916, xvii, 83-142.
- ⁵MARTLAND, H. S. Occupational poisoning in manufacture of luminous watch

- dials, general review of hazard caused by ingestion of luminous paint, with especial reference to the New Jersey cases, Jr Am Med Assoc, 1929, xcii, 466, 552-559
- ⁶ORDWAY, T, and GORHAM, L W Diagnosis and treatment of diseases of the blood, Oxford Monographs, 1929, ix, Oxford University Press, New York
- ⁷OSGOOD, E E Hemoglobin, color index, saturation index, and volume index standards, redeterminations based on the findings in one hundred and thirty-seven healthy young men, Arch Int Med, 1926, xxvii, 685-706
- ⁸OSGOOD, E E, and HASKINS, H D Relation between cell count, cell volume, and hemoglobin content of venous blood of normal young women, redeterminations of color index, volume index, and saturation index standards based on observations in one hundred cases, Arch Int Med, 1927, xxxix, 643-655
- ⁹AUB, J C, and others Lead poisoning, Med, 1925, iv, 1-250
- ¹⁰HARTMAN, F A, and BROWNELL, K A The hormone of the adrenal cortex, Science, 1930, lxxii, 76
- ¹¹MINOT, G. R and MURPHY, W P Treatment of pernicious anemia by a special diet, Jr Am Med Assoc, 1926, lxxvii, 470-476
- ¹²JONES, N W, PHILLIPS, B I, LARSELL, O, and NOKES, H T The hemopoietic effect of nuclear extractives in human anemias, Ann Int Med, 1929, ii, 603-621
- ¹³STURGIS, C C, and ISAACS, R Desiccated stomach in the treatment of pernicious anemia, Jr Am Med Assoc, 1929, xciii, 747-749
- ¹⁴OSGOOD, E E, and WILHELM, MABLE M Reticulocytes Proc Soc Exper Biol and Med, 1931, xxix, 53-54

A Comparative Study of the Use of Whole Liver, Liver Extract and Ventriculin*†

By HUGO A. FREUND, A B, M D, F A C P, and ALVIN E. PRICE, A B, M D,
Detroit, Michigan

THE use of various anti-anemic substances in the treatment of primary anemia is now well recognized and established in medical therapeutics. Although sporadic cases have appeared in the literature in which some form of liver therapy has failed, there is abundant evidence which demonstrates the undoubted value of anti-anemic substances. As to their comparative value, however, there is relatively little to be found which indicates any difference in response to them. Thus, Minot and his co-workers¹ report that they noted no difference in the reticulocyte response obtained in the feeding of either whole liver or liver extract. Ordway and Gorham² treated nineteen cases with liver and six with liver extract, and from their study concluded that both groups responded equally well. Davidson et al.³ arrived at a similar conclusion. In a discussion on the use of "Desiccated Stomach" in the treatment of pernicious anemia, Isaacs and Sturgis⁴ stated that they were unable to find a difference in the course of the remission, or in the response of the

neurologic lesions, with ventriculin therapy as compared to that found with the use of liver. Conner⁵ was also of the opinion that the results of treatment with "swine stomach" would compare favorably with those derived from the use of liver or liver extract.

Quite in contrast to the above studies are those of Schulten⁶ and Berglund et al.⁷, in which no hemopoietic response with liver extract was found, but in which a definite remission resulted with the use of fresh whole liver. The case study reported herein bears a striking resemblance to the above group except that in addition to the whole liver and liver extract used above, ventriculin (Parke, Davis & Company) was also among the preparations administered.

The patient under discussion had been under our observation on two previous occasions, and at both times was successfully treated with liver extract. At the time of his third admission to the hospital, he was in a state of relapse with a marked anemia. The administration of ventriculin, and later the use of liver extract, failed to produce any significant remission in the blood picture. It was not until the patient was given the juice of whole liver that a satisfactory erythropoietic

*From Department of Internal Medicine, Harper Hospital, Detroit, Mich.

†Received for publication, September 17, 1931.

response on the part of the bone marrow was obtained. Because of the rarity of such a comparative study in the same individual, and because of the unusual nature of the results obtained, it was thought advisable to report the case study in the hope that it might offer some aid in the treatment of those cases which appear refractory to the usual anti-anemic therapy

CASE SUMMARY

First Observation The patient, O B, male, aged 20, was first seen on the medical service in March, 1929. At the time of his first admission he complained of weakness, loss of weight, sore tongue and paresthesias of the hands and feet. Examination at that time revealed an emaciated, pasty appearing boy with a ptosis of the left eyelid, a corneal scar in the left eye and an atrophy of the tongue. The heart was negative except for an apical systolic murmur. The spleen was enlarged to about two fingerbreadths below the costal margin and was firm and tender. There were no objective neurological findings.

The blood picture was that of a primary anemia with hemoglobin, 65 per cent, red blood cells, 1,710,000, white blood cells, 9,150. The differential count revealed 76 per cent polymorphonuclears, 16 per cent lymphocytes, and 8 per cent mononuclears. Red cells showed anisocytosis and poikilocytosis. Gastric contents showed no free hydrochloric acid. The indirect Van den Bergh was slightly positive.

On the basis of the above findings a diagnosis of pernicious anemia was made and liver extract therapy instituted (vials IV—daily, equivalent to 400 gms fresh raw liver). As a result of this treatment the patient had a prompt, though comparatively small, reticulocyte response (56 per cent) and a very definite increase in the percentage of hemoglobin and in the number of red blood cells. Five weeks after the institution of the liver extract therapy, the hemoglobin rose to 85 per cent and the total red count became 4,000,000. Coincident with the remission in the blood pic-

ture, the patient gained weight and his symptoms disappeared.

During the following ten months he remained symptom free on one quarter pound of liver a day with occasional substitution of liver extract. At the end of this time, he became unable to purchase liver and as a result some of his former symptoms returned. His blood picture, however, remained normal (Abortive relapse of Isaacs⁸).

Second Observation During the second period of observation there was little in the general physical and laboratory findings which differed from those present at the time of the patient's discharge from the hospital ten months previously. After only a brief period of hospitalization his symptoms disappeared and he was again discharged on one vial of liver extract, three times daily.

For the following six months the patient continued on liver extract and remained in perfect health. At the end of this time, however, he became financially unable to purchase liver extract, and as a result he took no anti-anemic substance. During this time he lost weight, became weak and developed numbness and tingling of the hands and feet. In addition to this, he complained of nausea and vomiting. With these symptoms he re-entered the hospital.

Third Observation Physical examination on his third entrance to the hospital revealed little that was not found at the time of his first admission. There was obvious pallor and evidence of considerable weight loss. The ocular findings were as before and the atrophy of the tongue was still in evidence. The spleen was enlarged to the same extent as formerly but appeared to be less tender to palpation. There was no disturbance in the vibratory, or motion and position senses in the extremities. Reflexes were normal. Heart and lungs were negative.

Laboratory Data Blood count: Hemoglobin, 50 per cent, red blood cells, 2,500,000, color index, 11, white blood cells, 4,000, polymorphonuclears, 39 per cent, lymphocytes, 60 per cent, eosinophils, 1 per cent. Red cells showed poikilocytosis, anisocytosis and polychromatophilia. Diameter of red cells varied between 9.5 and 4

μ Reticulocytes, 0.4 per cent Blood fragility, beginning hemolysis, 0.4 per cent, complete 0.3 per cent Hematocrit study volume percentage of RBC = 29 Blood culture and blood Wassermann, negative Blood nitrogen, 28.6 mgs Blood sugar, 0.100 per cent Blood cholesterol, 143 mgs Blood platelets, 383,000 Bleeding time, four minutes Coagulation time, four and one-half minutes Van den Bergh, direct and indirect, negative Gastric analysis (with histamine), no free hydrochloric acid (three examinations) Urinalysis, negative Urobilinogen, positive Stool analysis, normally formed, no blood, ova or parasites X-ray examination gastro-intestinal, negative, chest, negative except for extensive root deposit with exaggerated trunk markings throughout both lung fields

CLINICAL COURSE

First Period During the first eighteen days of hospitalization the patient was given ventriculin (Parke, Davis & Company), the initial dose consisting of three vials daily, (30 gms) At the end of ten days the dose was increased to four vials, this being continued for eight days Because of persistent nausea and vomiting, an attempt was made to give this preparation by rectum (Vials VI, 60 gms), but this was unsatisfactory

During the period of ventriculin therapy there was no clinical improvement The nausea and weakness persisted The blood picture showed no appreciable change, the reticulocytes increasing to 0.9 per cent and the total red count reaching its highest peak of 2,500,000 on the tenth day, this representing a total gain of only 250,000 red cells The hemoglobin dropped from the original 50 per cent to 38 per cent on the eighteenth day The white count remained low throughout, the differential showing a constant lymphocytosis, on one occasion reaching 86 per cent The polymorphonuclear cells showed an almost constant shift to the left While the total blood count showed little or no change, a study of the blood smear revealed evidence of attempts at blood regeneration, i.e., stippling of red blood cells, normoblasts, etc

Throughout the entire period of ventriculin therapy the patient had a daily

temperature elevation varying from 99 to 100 Careful and repeated urinalyses, sinus and chest x-rays, etc., failed to reveal any evidence of infection or other cause for this febrile reaction

Second Period During the second period the patient was given liver extract (Lilly's No 343, one vial = 100 gms whole liver) starting with four vials a day and after two weeks increasing this to six vials daily The latter dosage was given for one week While under this therapy the blood picture showed little change The reticulocytes rose from 0.3 per cent at the beginning of the period to a maximum of 1.14 per cent on the eleventh day The red cell count increased from 1,230,000 to 2,020,000 on the sixth day, and then fell to 1,895,000 The hemoglobin increased from 38 to 48 per cent over the entire period of three weeks The leucocytes remained low throughout, only on one occasion reaching as high as 8,100 The blood smear showed evidence of blood regeneration with a tendency to a right shift of the leukemoid picture Throughout this period also, the patient continued to have an unexplained daily temperature elevation, although the general level was below that of the preceding period The general condition showed no appreciable improvement

Third Period Following the unsuccessful use of liver extract, first of three and then of six vials a day, the patient was next given the juice of one pound of whole liver daily The following day the reticulocyte count rose from 0.33 per cent to 0.5 per cent and on the third day it rose to 9 per cent The red count increased from 1,900,000 to 3,000,000 on the eighth day, the leucocyte and differential count remaining practically normal throughout The smear showed evidence of progressive blood regeneration

On the fifteenth day of "liver juice therapy" it became obvious that the patient had reached a standstill in his blood picture The hemoglobin had attained a level of 78 per cent and the red count had already started to drop slightly The juice of three pounds of liver was then given daily with a resulting progressive increase in the hemoglobin and red count On the seventh day the hemoglobin rose to 92 per cent and the red count reached 4,720,000 The rest

of the blood count was normal—the smear presenting a normal blood picture

Coincident with the elevation in the blood count there occurred a distinct improvement in the clinical condition. Appetite became progressively better, nausea and vomiting ceased, and strength returned. The temperature elevation persisted.

An attempt to decrease the dose of liver juice to that of two pounds daily, resulted in a prompt drop in the blood count and a recurrence of a characteristic group of symptoms, viz, numbness and tingling of fingers and stiffness of the neck. This picture was seen on several subsequent occasions during a relapse in the blood picture. Because of this the dose was increased to its former level with a resulting prompt improvement in the blood picture and in the clinical condition of the patient.

Realizing the impracticability of taking whole liver juice after leaving the hospital it was thought advisable to try some preparation which would be more conveniently used by the patient. Although liver extract had previously failed it was tried again hoping that it would maintain the blood level produced by the whole liver. The use of three vials a day was promptly found to be inadequate, and the dose was therefore increased to six vials. This resulted in a prompt return of the blood picture to its former level. Two weeks later it became necessary to increase this to eight vials daily because of a drop in the blood count and a return of the above described symptoms so characteristic in this case of a falling blood picture. This proved to be adequate for only two weeks, and at the end of this time the clinical condition of the patient again started to fail. Because of this the liver extract was supplemented by whole liver (one-third pound daily), this resulting in prompt improvement in the general condition. After one month on this "combined therapy" the liver was omitted from the diet entirely. Ten days later the amount of liver extract was decreased to six vials without any change in the blood picture or in the clinical condition of the patient. At the present writing this dosage has been further reduced to three vials a day. The blood count at

present is hemoglobin, 97 per cent, red blood cells, 5,120,000 (on three vials a day for two weeks)

[It has subsequently come to our attention that this patient had another relapse during which he was cared for in the Simpson Memorial Institute for Medical Research, Ann Arbor, Michigan. While in this institution he was successfully treated with intravenous liver extract after the use of stomach and liver preparations by mouth had failed.]

COMMENT

In a review of the above case study several facts are worthy of note. One is impressed with the successful use of whole liver after both liver extract and ventriculin failed. There is also noted the necessity for large and increasing doses of anti-anemic substances in order to obtain the desired blood level.

The first observation is of particular interest in this case when it is recalled that the patient under consideration had previously responded well to three vials of liver extract a day, and even at the present time is satisfactorily controlled on similar quantities of the same preparation. In the absence of complicating factors such as infection, etc., it is thought that such a variation in response at different periods can best be explained on the basis of a different reactive state of the bone marrow during the various remissions.

The reason for the success of whole liver in this case after the other products had failed is not at once apparent although several explanations suggest themselves. One might first question the potency of the products used. The ventriculin was supplied by the manufacturers, Parke, Davis & Company, for experimental purposes. The liver extract used was the standard

product of Eli Lilly & Company (No 343)

A second explanation lies in the possibility of an inadequate dosage of these products. Unfortunately, the administration of larger quantities of ventriculin was prevented by the patient's persistent nausea and vomiting. Final conclusion, therefore, should not be drawn regarding the efficacy of this product in this case since only the minimum amount could be used. It will be noted, however, that the usually required dosage was administered without success. A significant elevation of the reticulocyte count did not occur. With liver extract, although a definite reticulocytosis was produced, the administration of nearly twice the quantity ordinarily required was insufficient to produce any appreciable increase in the red blood cell count. In contrast to this, the use of proportionately less fresh whole beef liver as liver juice, was sufficient to produce not only the same reticulocyte response as that resulting from liver extract, but a definite elevation of the total red count and percentage of hemoglobin as well.

A third explanation, i.e., the presence of an infection, is suggested by the persistent fever and the "left shift" of the neutrophilic elements of the blood. That an infection may alter the response of the blood forming organs to anti-anemic substances is illustrated in the recent case report of Smithburn and Zerfos⁹. In an earlier publication by Minot, Murphy and Stetson¹, the depressant action of infections on bone marrow was also emphasized. In this case, as already stated, no focus of infection could be found. *Of further importance in this*

connection is the fact that the fever was not confined to the period of ventriculin and liver extract therapy, but continued throughout the administration of whole liver juice as well.

The failure of the above suggestions to account for the results in this case, leads one to suspect that the explanation may lie in the composition of the whole liver in contrast to that of liver extract or ventriculin. The question, therefore, arises—does whole liver contain some principle not present in either of the other two substances, or present in lesser quantity, which renders it more effective in its action on the hemopoietic system when the latter is in a state of marked depletion? That some difference does exist between the effect of these various substances on blood forming tissue is suggested by the eosinophilia resulting from the use of whole liver in contrast to the absence of this response with the use of liver extract (Meulengracht and Holm¹⁰ and others^{11,12}). The absence of this effect with ventriculin has also been noted (Goldhamer¹³). Likewise, the special effect of whole liver on hemoglobin formation as compared to that resulting from the use of liver extract is further evidence of the difference of effect of these substances (Isaacs, Sturgis and Smith,¹⁴ and others¹⁵). To explain a variation in erythrocytic response on the same basis is, of course, conjectural, but would nevertheless appear worthy of consideration.

The second observation mentioned above in which it was noted that larger quantities of anti-anemic substances were required for adequate stimulation of the bone marrow has already been noted by others. Thus

Minot and his co-workers¹ were able to produce a secondary reticulocyte response together with a marked increase in the total red cell count after feeding larger quantities of liver pulp. In our case there developed a secondary reticulocyte response immediately upon the administration of fresh whole liver juice and simultaneously with this, a definite elevation in the total red count and percentage of hemoglobin. Further increase in the amount of liver was then required to attain the maximum blood level desired. As already stated in the discussion of the case early attempts at decreasing the quantity of whole liver as well as substituting liver extract for the latter were unsuccessful in maintaining the desired blood picture. It was not until two and one-half months after the institution of liver therapy that substitution by liver extract became possible. Such an observation as this, in the absence of complicating factors, would lead one to postulate that the response of the

bone marrow in some cases, and at certain periods, is dependent upon the "quantity" of the anti-anemic substance administered as well as the "quality" as already discussed above.

SUMMARY

A case of primary anemia is presented which failed to respond to both ventriculin and liver extract, but which later responded satisfactorily to the juice of whole liver.

Attention is also drawn to the fact, that larger and increasing doses of anti-anemic substance were required to produce and maintain the desired blood level.

It is suggested that in those cases which prove resistant to the usual "anti-anemic extracts", whole liver be given a trial. It is further suggested that large quantities of the anti-anemic substance be given before the case be considered refractory.

We wish to thank Mr. Emil Schleicher of Parke, Davis and Company, for his technical and material assistance in the study of this case.

REFERENCES

- ¹MINOT, G., MURPHY, W., and STETSON, R. The response of the reticulocytes to liver therapy, particularly in pernicious anemia, *Am Jr Med Sci*, 1928, clxxv, 581-599.
- ²ORDWAY, T., and GORHAM, L. W. The treatment of pernicious anemia with liver and liver extract, *Jr Am Med Assoc*, 1928, xci, 925-928.
- ³DAVIDSON, S., MCCRIE, J. G., and GULLAND, G. L. The treatment of pernicious anemia with liver and liver extracts, *Lancet*, 1928, i, 847-852.
- ⁴ISAACS, R., and STURGIS, C. Some newer remedies in the treatment of pernicious anemia—desiccated stomach, *Jr Am Med Assoc*, 1930, xcv, 585-587.
- ⁵CONNER, H. M. The treatment of pernicious anemia with swine stomach, *Jr Am Med Assoc*, 1930, xciv, 388-390.
- ⁶SCHULTEN, H. Über Misserfolge der Lebertherapie der perniziösen Anämie und ihre Ursachen, *Munch med Wchnschr*, 1930, lxxvii, 59-61.
- ⁷BERGLUND, H., WATKINS, C., and JOHNSON, R. Significant difference in response of pernicious anemia to fetal calf and beef liver feeding, *Proc Soc Exper Biol and Med*, 1928, xlv, 834-835.
- ⁸ISAACS, R. Systemic relapses during liver induced hemopoietic remissions in pernicious anemia, *Am Jr Med Sci*, 1929, clxxviii, 500-505.
- ⁹SMITHBURN, K. C., and ZERFOS, L. G. The inhibitory action of infection and

- fever on the hematopoietic response in a case of pernicious anemia, *Ann Int Med*, 1931, iv, 1108-1111
- ¹⁰MEULENGRACHT, E., and HOLAR, S. Eosinophilia in liver diet, *Am Jr Med Sci*, 1930, clxxv, 199-208
- ¹¹MINOR, G. R. The treatment of pernicious anemia with liver or an extractive fraction of liver, *Tr Coll Phys*, 1927, xlix, 144-153
- ¹²BERGLUND, H. Liver diet in pernicious anemia, *Ann Int Med*, 1928, ii, 471-473
- ¹³GOLDHAWER, S. M. Non-development of eosinophilia in pernicious anemia patients treated with desiccated stomach, *Ann Int Med*, 1931, iv, 1105-1107
- ¹⁴ISAACS, R., STURGIS, C., and SMITH, M. Treatment of pernicious anemia, *Jr Am Med Assoc*, 1928, xci, 1687-1690
- ¹⁵MINOR, G. R., COHN, E. J., MURPHY, W. P., and LAWSON, H. A. Treatment of pernicious anemia with liver extract, effects upon the production of immature and mature red blood cells, *Am Jr Med Sci*, 1928, clxxv, 312-317

If You Have a Persistently High Blood Pressure

“IF YOU have passed the milestone of middle life, you should develop a hobby of some type, which is interesting, pleasant, and not a part of your daily employment or thought. Secondly, you should teach an understudy, if you are in business, to take charge of your affairs from time to time, so that when that day comes when you should play a less active rôle in the management of your affairs than formerly, it will lessen that inevitable anxiety which will confront you when you realize that your endurance and physical fitness are becoming less.

“Finally, if you represent that large group of despondents who have high blood-pressure disturbances as a part of their general body let-down, allow me to say a word of cheer. If your body were a mechanical thing, manipulated by a motor, with bearings and joints that were dependent upon protection, adjustment, and lubrication in a manner similar to that of the automobile, and if life's journey were traveled along a rough and rugged road which ended in precipitate heights, and you wished to reach life's goal of matured years, you could do any one of the following three things: Lighten your daily loads, protect the wear and tear of your machinery, or smooth out the roadbed.”

(From *How's Your Blood Pressure?* by CLARENCE L. ANDREWS, M.D., F.A.C.P., The Macmillan Company, 1931.)

Raynaud's Disease Affecting Men*†

By EDGAR V ALLEN, M D , F A C P , and GEORGE E BROWN, M D , F. A C P ,
Rochester, Minnesota

OF the vasospastic disorders affecting the peripheral circulation, of which Raynaud's disease represents the most typical form, the distribution by sex is the reverse of that found in organic disease of the peripheral arteries.² Various writers have given the incidence of Raynaud's disease in the female as from 60 to 90 per cent, and a critical survey of the reports of cases offered as examples of Raynaud's disease in the male has given evidence of an exceedingly high proportion of erroneous diagnoses.¹ Many such cases represented classical examples of thrombo-angitis obliterans.

The criteria for diagnosis of Raynaud's disease are as follows (1) episodes of change in color, of the vasospastic type, excited by cold or emotion, (2) bilaterality, (3) presence of normal pulsations in the palpable arteries, (4) absence of gangrene, or its limitation to minimal grades of cutaneous gangrene, (5) absence of any primary disease which might be causal, such as cervical rib or organic disease of the nervous system, and (6) symptoms of two years or of longer duration.

*From the Division of Medicine, The Mayo Clinic, Rochester, Minnesota

†Submitted for publication, December 9 1931

The first four criteria were succinctly stated by Raynaud.¹ The fifth and sixth have been added by us to emphasize the necessity of eliminating causes to which the vasomotor symptoms might be secondary.

PRESENT STUDY

A diagnosis of Raynaud's disease, uncomplicated by scleroderma or trophic changes, and unassociated with arthritis, has been made in 150 cases at The Mayo Clinic. The characteristic symptoms of vasomotor episodes of discoloration of the skin of the fingers or toes, occurring bilaterally and intermittently, were present in every instance. Males comprised seventeen of these 150 cases (12 per cent), but in only seven of these seventeen (5 per cent of 150) could the diagnosis be substantiated on the basis of additional requirements of long duration of symptoms and of demonstration of absence of such conditions as cervical rib, and organic disease of the peripheral arterial system.

In each of the remaining ten cases (table) the diagnosis "probable Raynaud's disease" was made, in each instance some objection could be offered to the diagnosis of true Raynaud's disease. These objections are as follows: in cases 1 and 8 the duration of symptoms was only four and

six months, respectively, in case 2, rudimentary cervical rib was demonstrated roentgenologically although it probably was not of significance, in cases 3, 4, 5, 6, 7, 8, 9, and 10, specific notation as to presence of pulsation was lacking, and in case 6, there was no notation as to the duration of symptoms. Gross evidence of obstructive arterial disease was not present in any of the cases. However, in those cases in which there was no specific mention of pulsations in the peripheral arteries, the possibility of the presence of arterial disease characterized by occlusion cannot be excluded.

In seven of the seventeen cases (41 per cent) there was evidence of functional or neurotic disturbances, such as dizziness, nervousness, flatulence, vague gastric distress, biologic inferiority, or cardiac neurosis. The incidence of these disturbances exceeds by 17 per cent that found in a group of females with Raynaud's disease.

The ages of sixteen of the patients at the onset of symptoms were as follows: first and second decades of life, eight cases; third decade, three cases; fourth decade, five cases. In the remaining case the age at onset of the symptoms was not known. This emphasizes the fact that Raynaud's disease is a condition of youth and middle age. In a series of 115 females with uncomplicated Raynaud's disease, 77 per cent of the patients manifested their first symptoms before the age of forty years.

Data on height and weight were available in fifteen of the seventeen cases. Comparison with standard tables based on age and height and allowing a variation of plus or minus 10 pounds, disclosed that three of the

patients (20 per cent) were overweight, seven (47 per cent) were of normal weight, and five (33 per cent) were underweight. In this small series of cases, such a distribution is probably of no significance. For comparison among women with Raynaud's disease, the thin, asthenic type of person is more frequently seen, of 112 women, 50 per cent were underweight, 35 per cent of normal weight, and 15 per cent of more than normal weight.

Forty-seven per cent, eight of the seventeen men, were unmarried. For comparison 40 per cent of 121 women with the same type of Raynaud's disease were unmarried. The comparative youth of a number of the male patients doubtless accounts for their being unmarried.

COMMENT

A convincing explanation of the low incidence of Raynaud's disease among men, as compared with women, has not been offered. Equally as difficult of explanation is the comparatively high incidence (98 per cent) among men² of thrombo-angitis obliterans. Considerable weight in diagnosis can be given to the predilection of these two diseases for the respective sexes. If a novice in the diagnosis of peripheral vascular diseases were shown 100 women and 100 men known to be affected with either Raynaud's disease or thrombo-angitis obliterans, he could arrive at the correct diagnosis in 90 per cent of the cases with no further knowledge than that of the sex of the patients. The presence of the other 10 per cent, however, emphasizes the necessity of careful development of the clinical history and of examination with assiduous attention to details.

Our studies have indicated that men

TABLE
SUMMARY OF CASES OF RAYNAUD'S DISEASE AFFECTING MEN

Diagnosis	CASE	AGE, YEARS	EPISODES OF DISCOLORATION						
			REGION		DURATION, YEARS	TYPE			
			FINGERS	TOES		PALLOR	RUBOR	CYANOSIS	BILATERAL
True Raynaud's Disease	1*	24	Yes	Yes	10	Yes	No	Yes	Yes
	2*	48	Yes	Yes	3	Yes	Yes	No	Yes
	3*	49	Yes	Yes	5	Yes	No	No	Yes
	4*	19	Yes	No	4	Yes	No	Yes	Yes
	5*	39	Yes	No	20	Yes	No	No	Yes
	6*	18	Yes	Yes	9	Yes	Yes	No	Yes
	7*	28	Yes	No	12	Yes	Yes	Yes	Yes
Probable Raynaud's Disease	1*	37	No	Yes	0 33	Yes	No	No	Yes
	2*	43	Yes	No	1 5	Yes	No	Yes	Yes
	3**	54	Yes	Yes	10	Yes	No	No	Yes
	4**	40	Yes	No	30	No	No	Yes	Yes
	5**	49	Yes	No	6	Yes	No	No	Yes
	6**	33	Yes	No		Yes	No	No	Yes
	7**	54	Yes	Yes	40	Yes	No	Yes	Yes
	8***	30	Yes	No	0 5	Yes	No	No	Yes
	9**	28	Yes	No	5	Yes	No	Yes	Yes
	10**	26	Yes	No	10	Yes	Yes	Yes	Yes

* Denotes normal pulsations in the radial, ulnar, dorsalis pedis, and posterior tibial arteries

** Denotes no information regarding pulsation

*** Denotes normal pulsation in the radial artery and no information regarding pulsation in the ulnar, dorsalis pedis, and posterior tibial arteries

are particularly subject to organic derangement and women particularly to functional derangement of the peripheral vascular system. Whether this is because men and women live and work at different paces, whether the reason is that women secrete a protective hormone denied to men, or whether the explanation lies in the different tendency of members of the two sexes to acquire diseases of which neurosis is an element is not known.

SUMMARY

The condition of seven men met all the requirements for a diagnosis of

Raynaud's disease. In an additional ten cases, the diagnosis was probable Raynaud's disease. Of all patients affected with uncomplicated Raynaud's disease, about 5 per cent were men (seven cases of 150). In an additional 7 per cent of uncomplicated cases, also (ten cases of 150), the patients were men, in this 7 per cent of cases, the diagnosis seemed warranted but some objection could be raised to it. Possible reasons for the predilection of peripheral vascular diseases for one or the other of the two sexes are mentioned in the paper.

REFERENCES

ALLEN, E. V., and BROWN, G. E. Raynaud's disease: a critical review of minimal requisites for diagnosis. *Am Jour Med Sc*, 1932, *clxxxiii*, 187-200.

HORTON, B. T., and BROWN, G. E. Thrombo-angitis obliterans affecting women. Personal communication.

Does Liver Therapy Benefit the Diabetic?*†

By ELMER L. SEARINGHAUS, M D, F A C P, *Madison, Wisconsin*

AS a consequence of the reports of Blotner and Murphy¹ a number of trials have been made in this hospital with liver therapy for diabetes mellitus. The first of these was made with feeding of whole liver, 180 grams daily, to two cases of clinically unvarying tolerance. The results gave no encouragement at that time (1929). In July, 1930, our attention was directed to the possible merits of a mixture of an extract of horse liver, horse blood, with hypophosphites, alcohol, and saccharin, referred to below as "liver mixture". The manufacturers of a certain commercial horse liver and blood mixture had reports from two clinicians that this preparation had apparently been of marked benefit to some diabetic patients. This mixture has been prepared and marketed for the treatment of anemias other than pernicious anemia. Consequently the manufacturers prepared the special mixture described above, omitting the sugar and glycerol from the usual commercial formula. Late, on request they supplied also simple aqueous liver extracts, preserved with 16 per cent alcohol, and dried residue from aque-

ous liver extract. Since careful clinical records were not available from the clinicians who had first reported on the ordinary mixture, they were eager to have dependable studies of such products made before any attempt was made to enter into commercial production. These materials were made under the personal supervision of the chemist at the packing plant. The commercial use of meat from the horse has been developed to a large extent by this firm, both for foreign trade and for the production of compounded rations for small animals in this country. The selection of animals and the plant conditions are apparently excellent. This report therefore applies entirely to the use of material from the liver of the horse.

The first patient studied was a 15 year old girl who had been diabetic for four years. She required 105 units of insulin daily with a maintenance diet. An attempt was made to replace insulin with "liver mixture", but a precomatose condition was apparent in 24 hours after insulin withdrawal. A few days later an attempt was made to reduce the insulin dose by substituting the oral preparation for 20 units of insulin. When 85 units were combined with 15 c c of "liver mixture" before each meal for one week there was no evidence of benefit. An increase to 30 c c three times daily was

*From the Department of Medicine and the Wisconsin General Hospital, University of Wisconsin, Madison, Wisconsin.

†Received for publication, August 10, 1931.

no better After a nine day interval a simple aqueous liver extract was tried for seven days without benefit Thereupon a liver press juice was substituted for six more days. Throughout this period 95 units of insulin were administered daily, in spite of which there was slight ketosis and glycosuria as marked as when insulin was given alone.

At the same time a young man was treated with "liver mixture" as soon as it had been found that on a standard 1525 calorie diet he excreted 144 to 165 grams of sugar daily With the use of 30 c c of the oral preparation before each meal for three days his glycosuria rose to 23.8 to 27.5 grams, with unabated ketosis With the use of 30 units of insulin daily he was free from glycosuria and ketosis while using a 2270 calorie diet

An emaciated diabetic man of 40, weighing 100 pounds, was found to maintain his weight on a 1965 calorie diet While using 10 units of insulin daily he had only traces of glycosuria, with infrequent positive nitroprusside tests on the urine Blood sugar values of 187 to 199 mg per 100 c c were observed in the morning Addition to this routine of "liver mixture" in doses of 15 c c three times daily for five days, then of 30 c c before each meal for six days, was ineffective There were no consistent changes in glycosuria, weight, or the level of blood sugar Ketosis did not occur during the last week of this trial, but it was absent except for three days in the following three weeks when insulin alone was used at the same level as before

A 57 year old man with dry gangrene of several toes was found to lose 147 to 182 grams of sugar

while on a 1525 calorie diet There was no ketosis The use of "liver mixture", 15 c c before meals for six days, was followed by an apparent improvement, with glycosuria less than six grams on four of the six days Use of the simple extract of liver in 15 c c doses for five days, in 30 c c doses for three days, and of the liver press juice in 30 c c doses for five days gave similar results When only the diet was used as treatment the result was just as good, with glycosuria continuing to vary from 3 to 8 grams daily During the period of observation the morning blood sugar had dropped from its original level of 200 mg to 80 mg six days after stopping liver press juice The use of insulin in two doses of 5 units each abolished all glycosuria This case had evidently made the usual improvement in sugar tolerance which must be attributed to dietary restriction alone The liver treatment cannot be considered responsible for even this slight improvement

It was considered possible that absorption of some insulin given by mouth might be facilitated by liver materials in a way similar to that claimed by Stephan² Therefore a trial was made by mixing insulin in a solution of the liver and blood extracts only, the materials used for making the "liver mixture" The patient was a male, aged 33, who required 52 units of insulin to remain free from glycosuria and ketonuria on a 2270 diet When the insulin was given in the tissue extracts by mouth, the dose and time being the same, glycosuria reappeared The insulin doses were doubled without any benefit The loss of sugar was similar

during the periods with such therapy and during intervals when only the liver and blood extract were administered, or for two days without therapy. A return to the use of 52 units of insulin promptly restored the balance of the patient. There is no reason to conclude that the insulin given by mouth to this patient had any effect.

Following this series of negative results it was thought best to try an exact duplication of some of the work reported by Blotner and Murphy.¹ An aqueous extract of liver was heated to 80°C, and the precipitated material was dried in an air current of 40° to 50°C. This treatment is said by the above authors to leave the activity of their preparations unaffected. The dry material from one pound of liver was estimated to be 24 grams. The use of 8 grams of this powder with each meal was easily arranged, this should be the equivalent of the ingestion of one pound of liver daily so far as the substances in such a preparation are concerned.

A male patient, aged 23, using 1965 calories and 35 units of insulin had slight morning glycosuria, minimal amounts of acetone in the urine, and his blood sugar was 143 and 140 mg on two mornings. The use of 24 grams of dried liver powder as above made no change in the urine findings, the blood sugar after two days was 136 mg in the morning, there were no insulin reactions.

Another patient, aged 14, required the same insulin dose and the same diet, but had no traces of acetone in the urine. In this case the insulin was withheld and the 24 grams daily of liver powder administered. Glycosuria and ketonuria reappeared and the

blood sugar rose from 120 mg to 167 mg. The liver powder was continued and the insulin doses were raised gradually. Not until after two days on the original dose of 35 units was the glycosuria and ketonuria abolished.

Further trials of this powder were made by giving it with the usual breakfast and insulin, following which series of blood samples were taken. On the preceding day a control observation was made. The protocols for two such cases are given in the table. It seemed in patient "M" that the blood sugar was less variable on the morning when the liver powder was given. The advantage is certainly not great. In the case of "A" the difference between the two curves is within the limits of variation commonly seen on successive days.

For the supply of materials as desired and for the cost of hospital study for these cases grateful acknowledgement is made to the Chapel Bros, Inc, of Rockford, Ill. Their chemist, Dr A. E. Meyer, reports that he had made numerous attempts to detect activity of these and other liver preparations in rabbits, normal dogs, totally and partly depancreatized dogs, but without any convincing evidence of antidiabetic action.

We fail to find evidence that there is antidiabetic activity in the "liver mixture" or in the alcoholic extracts of liver and blood, liver alone, or in a press juice prepared from horse liver. A dried powder of the heat precipitate from aqueous liver extract was tried by methods similar to those used by Blotner and Murphy, but without any favorable result. No explanation is suggested for the failure to confirm the work of these authors, but the re-

sults reported agree with the negative results of dePencier, Soskin, and Best,³ Soskin, Binswanger, and Strouse,⁴ as well as of Root⁵

TABLE OF BLOOD SUGAR VALUES
PATIENT "M"

TIME, HOURS	BLOOD SUGAR, mg PER 100 c c	
	USUAL DAY	WITH LIVER POWDER, 16 gm
0	136	125
Insulin, 15 U Breakfast		
1	97	128
2	175	123
3	117	
4	73	115

PATIENT "A"

TIME, HOURS	BLOOD SUGAR, mg PER 100 c c	
	USUAL DAY	WITH LIVER POWDER, 16 gm
0	160	179
Insulin, Breakfast		
1	144	163
2	156	162
3	121	123
4	118	108

Breakfast, both days Protein, 18, Carbohydrate, 17, Fat, 51 grams

REFERENCES

- ¹BLOTNER, H, and MURPHY, W P Effect of certain liver extracts on the blood sugar of diabetic patients, Jr Am Med Assoc, 1930, xciv, 1811-1816
- ²STEPHAN, R Über die Wirkungsart des gallensauren Insulins bei subkutaner Anwendungsform, Deutsch med Wchnschr, 1930, lvi, 88-97
- ³DE PENCIER, M T, SOSKIN, S, and BEST, C H Effect of liver on blood sugar level and on sugar excretion of depancreatized dogs, Am Jr Physiol, 1930, xciv, 548-552
- ⁴SOSKIN, S, BINSWANGER, H F, and STROUSE, S Jerusalem artichokes and liver in the treatment of diabetes mellitus, Jr Clin Invest, 1931, x, 169
- ⁵ROOT, H F Diabetes and pernicious anemia, Jr Am Med Assoc, 1931, xcvi, 928-933

Primary Sclerosis of the Pulmonary Artery*†

Report of a Case

By EDGAR R. PUND, A.B., M.D., F.A.C.P. and THOMAS B. PHINIZY, M.D.,
Augusta, Georgia

ARTERIOSCLEROSIS of the pulmonary artery may be primary or secondary. The primary type is rare and affects the small arteries and the arterioles of the pulmonary circulation with or without accompanying arteriosclerotic changes in the larger branches. The sclerotic changes in the small arteries produce narrowing and even obliteration of the lumen, thereby causing an increase in the pulmonary blood pressure followed by dilation and hypertrophy of the right side of the heart and finally cardiac failure. There are no antecedent pulmonary or cardiac changes, and, according to Steinberg,¹ the use of the term primary sclerosis of the pulmonary artery is justified only when arteriosclerosis of the greater circulation is minimal or entirely absent.

Secondary sclerosis of the pulmonary artery is considered to result from mitral disease, cardiac abnormalities, emphysema, pleural adhesions, chronic bronchitis, or it may be incidental to a generalized arteriosclerosis.

In the periodical literature certain cases of sclerosis of the pulmonary

artery are referred to as Ayerza's disease. It is probable that some of these are primary and some secondary. The syndrome, Ayerza's disease, characterized by dyspnea, cyanosis, polycythemia and hypertrophy of the right heart, was described by Ayerza in 1901 in his lectures at Buenos Aires. He recognized the pathology of these cases as arteriosclerosis of the pulmonary artery, and spoke of the patients as "black cardiacs." Syphilis is considered a prominent etiological factor in this disease, but two opposing views are advanced with regard to the time of onset of the sclerosis, the discussion turning on whether the disease is primarily caused by the arteriosclerosis of the pulmonary artery, or whether the sclerosis is secondary to antecedent changes in the lung. In Ayerza's disease, Escudero² maintains that chronic syphilitic bronchitis is the first phase, characterized by polycythemia, and that the second phase presents, in addition, sclerosis of the pulmonary artery, peribronchial sclerosis and hypertrophy of the right heart. This view receives the support of Brachetto-Brain³ who thinks that the term, Ayerza's disease, should be restricted to cases in which each of the two phases is complete, the chronic broncho-pneumopathy with pro-

*From the Medical Department of the University of Georgia, Augusta, Georgia.

†Received for publication, August 10, 1931.

nounced polycythemia and the chronic cardio-angiopathy with insufficiency of the right heart. In a review of cases of Ayerza's disease, Cheney⁴ also states that a definite preliminary stage is apparently necessary for the final development. This essential antecedent is a chronic bronchitis of from one to twenty-five years duration; and Staffieri⁵ defines Ayerza's disease as a condition that occurs in young people or persons of mature age whose history reveals a bronchial affection, extending over a long period of time, accompanied by bronchopulmonary sclerosis and emphysema and a sclerosis of the pulmonary artery. The possibility of advanced secondary sclerosis should be borne in mind in considering cases of Ayerza's syndrome, because secondary sclerosis, while usually confined to the larger branches of the pulmonary artery, may in advanced cases affect the smaller arteries and give rise to the same symptoms that are produced by primary sclerosis.

Arrillaga,⁶ however, concludes that in Ayerza's disease, sclerosis of the pulmonary artery is primary and due to the *Spirochaeta pallida*, and that the arterial changes may or may not be accompanied by lesions in the bronchi and lungs, and that when lesions occur in the bronchi and lungs they are secondary to the sclerosis of the pulmonary arteries. Since Ayerza's disease is a term that has probably been used to designate both primary and severe secondary sclerosis of the pulmonary artery, it is probably better to distinguish cases as primary or secondary.

In the pulmonary artery arteriosclerotic changes of a moderate degree are not uncommonly seen at the nec-

ropsy table, incidental to a generalized arteriosclerosis or as a result of chronic cardiac and pulmonary lesions, and according to Warthin⁷ such secondary changes are without clinical significance. Cheney,⁴ Miller,⁸ and Rosenthal⁹ distinguish primary and secondary arteriosclerotic changes in the pulmonary artery, in the primary type the smaller arteries are affected and in the secondary type the medium-sized and larger vessels are involved. Hare and Ross,¹⁰ in a review of the literature on sclerosis of the pulmonary artery, admit the occurrence of sclerosis as a complication of some antecedent cardiac or pulmonary condition, but they have collected twenty-three fully reported and authentic cases of a group in which the signs and symptoms were due to alterations in the pulmonary arteries themselves and in which no antecedent cardiac, pulmonary or bronchial lesions were present. To this group they add one of their own. They emphasize in the primary type the occurrence of obliterative endarteritis of the small arteries which may be followed by dilation and atheroma of the larger vessels. Rosenthal⁹ considers primary arteriosclerosis of the pulmonary artery a definite clinical entity and in a study of three cases, he found the most pronounced changes in the small arteries with evidence of progressive changes to the medium-sized and larger vessels. Giuffrida¹¹ distinguishes primary arteriosclerosis with productive changes, with a tendency to obliteration of the lumen of the small arteries, from secondary sclerosis that results from hypertension in the pulmonary circulation. In primary sclerosis changes in the medium-sized and

larger arteries need not necessarily occur^{9,10,12}

From this review it is evident that there is general agreement that sclerosis of the pulmonary artery may be secondary to changes in the heart and lungs, as mitral disease, emphysema, pleural adhesions and chronic bronchitis and also may be incidental to generalized arteriosclerosis. When sclerosis results from these conditions it is the main trunk and larger branches that are affected by the usual arteriosclerotic changes, intimal thickening and degeneration, medial degeneration and dilation of the vessels. These changes are as a rule without clinical significance, or are overshadowed by symptoms that are produced by the primary disease.

There is also recognized, as an entity, primary sclerosis of the pulmonary artery, affecting the small branches and obliterative in type, and this form is frequently accompanied or followed by arteriosclerotic changes in the larger branches. This type of arteriosclerosis has been compared to the arteriosclerosis affecting the small arteries of the kidney.¹ Primary sclerosis of the pulmonary artery is rare and unless borne in mind can easily be overlooked clinically. It is more common in males and occurs in adults usually before the sixth decade. The changes in the arteries are responsible for the signs and symptoms, such as cyanosis, polycythemia, dyspnea, hemoptysis, and frequently somnolence, vertigo and heart pain, anasarca and passive congestion of the liver, spleen, kidneys, and intestines follow, dilation of the right side of the heart and usually dilation of the trunk of the pulmonary artery are evident. Cyanosis may precede the cardiac failure by

several years.^{9,13} The specific findings at necropsy are arteriosclerosis of the small pulmonary arteries with varying changes in the alveoli and the bronchi of a fibrotic nature, and dilation and hypertrophy of the heart, particularly of the right side.

The etiology is not clear. Syphilis is given the prominent rôle by many authors,^{2,9,10,12,14,15} but the possibility of damage due to the inhalation of gases and particulate matter is suggested by Rosenthal,⁹ and in a case reported by Staffieri⁵ the patient was a heavy smoker. Rheumatism may also be considered an etiologic factor. Von Glahn and Pappenheimer¹⁶ have described changes in the arterioles of the lungs in cases of rheumatism and they state that the healed lesions may develop a picture that simulates obliterative endarteritis. In a case reported by Steinberg¹ the symptoms of sclerosis were preceded by a severe rheumatic polyarteritis. Giuffrida¹¹ thinks that the arteriosclerosis of the pulmonary circulation is of a constitutional type.

For the purpose of clarity it is convenient to consider sclerosis of the pulmonary artery as showing the same types of sclerosis that are observed in the systemic arteries. Syphilitic mesarteritis has been described,^{7,17,18} and the changes in the pulmonary artery are identical with those seen in the aorta, affecting as they do the first part of the pulmonary artery. Ordinary atherosclerosis occurs in the pulmonary artery and involves the larger branches, it is usually secondary to cardiac or pulmonary changes or incidental to a generalized arteriosclerosis. And finally an obliterative endarteritis of the smaller arteries occurs, which may or may not be associated

with lesions in the larger vessels. This type is of importance because of the resistance offered to the pulmonary circulation. Cardiac failure follows.

CASE REPORT

The patient, a negro male, 40 years of age, was first admitted to the University Hospital, October 11, 1926. He was a tinner by trade and was not accustomed to hard manual labor. There was a history of gonorrhea but not of syphilis. There was no history of respiratory infections prior to the onset of the present illness. His first symptoms were those due to congestive heart failure, and set in four months prior to his admission to the hospital. The chief complaints were shortness of breath, cough, hemoptysis, dizziness and swelling of the legs. At the time of admission the clinical picture was that of a severe cardiac break, with failure of the right side of the heart and the usual signs and symptoms of visceral passive congestion. After the establishment of compensation he was discharged November 6, 1926. There were thirteen subsequent admissions with only slight variations in the clinical picture. On one admission the red

cell count was 6,000,000, on three admissions, 5,000,000 or above, on four, 4,500,000 or above, and on six admissions, between 4,000,000 and 4,500,000. While the red cell count did not invariably present a true polycythemia, in our experience with negro cardiac patients, a red cell count of 4,000,000 is above the average. The blood pressure varied between 170/135 and 110/85, a constant low pulse pressure and high diastolic pressure. On three admissions cyanosis was recorded as an objective sign. This is of particular significance because the patient was a negro and cyanosis can easily be overlooked in one of this race. Right sided heart failure was dominant in all fourteen admissions. The blood Wassermann reaction varied; on two admissions it was ++++, once, +++, once, +, and negative at other times. On the eleventh admission the Kahn reaction was ++. In the early course of his illness, over a period of eleven months, he received three injections of neoarsphenamine of 0.6 gm each, without evident improvement. The cardiac breaks occurred at shorter intervals during the course of observation, and the establishment of compensation became increasingly difficult, necessitating massive venesections

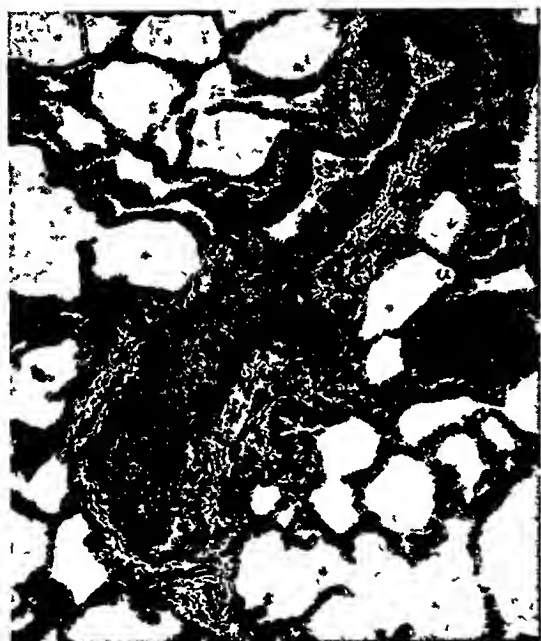


FIG 1 Longitudinal and cross section of a small pulmonary artery, the media is hypertrophied. There is a nodular thickening of the intima, almost occluding the lumen. $\times 250$



FIG 2 Cross section of a pulmonary arteriole. The intima is thickened and the lumen is almost obliterated. There are small areas of degeneration of the intima. $\times 500$

during the last three admissions. The patient succumbed March 11, 1931, approximately five years after the onset of symptoms. A necropsy was performed three hours after death.

Necropsy. The body was that of a well nourished negro male of some 45 years of age, 172 cm in length, and of estimated weight of 95 kg. There was considerable edema so that the skin was tense. The superficial veins of the neck were distended. A slight excess of clear fluid was found in the peritoneal, and both pleural, cavities. A few fibrous adhesions bound the bases of the lungs to the parietal pleura. The lungs were heavy and soggy, and crepitant throughout. The cut surfaces were dark red, much fluid blood flowed from the cut vessels. There was 100 cc of clear fluid in the pericardial sac. The heart weighed 675 gms. All chambers were dilated and filled with blood, on the left side fluid, and on the right coagulated. The endocardium was smooth but in the left atrium and ventricle it was slightly thickened. Of the valves there was nothing noteworthy. The measurements in centimeters of the valve orifices were as follows: aortic, 7, pulmonary, 7.5, mitral, 12.5, and tricuspid, 15 cm. The wall of the left ventricle was

17 cm in thickness and of the right ventricle, 0.5 cm. A few yellow patches were seen in the intima of the aorta, increasing in number downward. The wall of the inferior vena cava was noticeably thickened. A few raised yellow patches were seen in the intima of the coronary arteries. There was passive congestion of the liver, spleen, kidneys, and intestines.

Microscopical sections revealed nothing noteworthy except in the lungs. The most striking change in the sections from the lungs was the prominence of the small arterioles. They were tortuous and the walls were thickened, the thickening being due to an increase in the width of the media. Both the muscle and the elastic tissue of the media were hypertrophied. The lumina were narrowed. In some of the smaller arteries and in the arterioles there was an increase in the thickness of the intima due to fibrosis. Occasionally the lumen of a small arteriole was almost obliterated by a proliferation of cellular connective tissue, in which were small endothelial lined spaces. Rarely thrombi were observed. The adventitia of the arteries and the veins was increased. A few small veins contained thrombi. There was an increase of the connective tissue of the walls

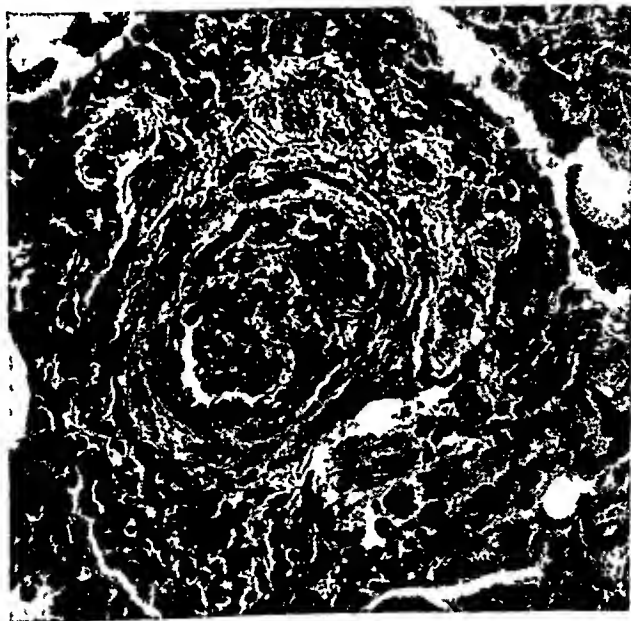


FIG 3 Cross section of a pulmonary arteriole. The lumen is obliterated by connective tissue which contains vascular spaces. $\times 500$

of most of the alveoli and sometimes the capillaries were obscured, the wall appearing as an avascular thin layer of hyaline connective tissue. The connective tissue about the bronchioles was increased, the lumina of the bronchioles narrowed, and the folds of the mucosa exaggerated. The muscularis of the bronchioles was hypertrophied. After prolonged search no *Spirochaeta pallida* were found in sections from the lungs.

COMMENT

From the history, clinical course and the pathology of this case the term primary sclerosis of the pulmonary artery is justifiably used. Such changes as were seen in the bronchi, lungs and

heart were secondary to the sclerosis of the arteries. On some occasions the Wassermann reaction was positive but no specific lesions were found at necropsy and, although the necropsy was performed soon after death, *Spirochaeta pallida* were not found in the lungs or in the lesions of the arteries of the lungs. There was no significant etiologic factor brought to light in the history.

Congenital hypertrophy of the media or faulty development may predispose the small pulmonary arteries to the obliterative changes that are observed in these cases.

REFERENCES

- ¹STEINBERG, U. Systematische Untersuchungen über die Arteriosklerose der Lungenschlagadern, zur Frage der primären Pulmonalsklerose, Beitr z path Anat u z allg Path, 1929, lxxxii, 443-463.
- ²ESCUERO, P. Enfermedad de Ayerza, Rev Soc de med int, 1925, 1, 701-820.
- ³BRACHETTO-BRAIN. Concepto anatómo-patológico de los cardíacos negros de Ayerza, Rec Soc, de med int, 1925, 1, 821-931.
- ⁴CHENEY, G. Ayerza's disease, report of two cases, Am Jr Med Sci, 1927, clxxiv, 34-45.
- ⁵STAFFIERI, D. Enfermedad de Ayerza, Rev méd del Rosario, 1929, xix, 437-446.
- ⁶ARRILLAGA, F. C. Esclerosis de la arteria pulmonar, Semana med, 1924, xxxi, 60-62.
- ⁷WARTIIN, A. S. Syphilis of the pulmonary artery syphilitic aneurysm of left upper division, demonstration of Spirochete pallida in wall of artery and aneurysmal sac, Am Jr Syph, 1917, 1, 693-711.
- ⁸MILLER, H. R. Sclerosis of pulmonary artery and its branches, Med Clin N Am, 1925, ix, 673-716.
- ⁹ROSENTHAL, S. R. Sclerosis of the pulmonary artery and arterioles clinical pathologic entity, Arch Path, 1930, x, 717-739.
- ¹⁰HARR, D. C., and ROSS, J. M. Syphilitic disease of pulmonary arteries, with account of case, Lancet, 1929, ii, 806-812.
- ¹¹GIUFFRIDA, E. Recerche sull' arteriosclerosi nelle piccole arterie del polmone, Arch di pat, e clin med, 1929, ix, 77-110.
- ¹²ACHARD, C. Cardiaques noirs et artérites pulmonaires, Bull méd, 1930, xlv, 409-413.
- ¹³SCHIASSI, F. Arteriosclerosi dell'arteria polmonare, Arch di pat e clin med, 1930, ix, 526-541.
- ¹⁴KONSTAM, G. L. S., and TURNBULL, H. M. Syphilis of lung with pulmonary arteritis (Ayerza's disease), Lancet, 1929, ii, 756-761.
- ¹⁵CAUSSADE, G., and TARDIEU, A. Un cas d'artérite syphilitique du poumon (cardiaque noir). Considerations sur la bronchite chronique syphilitique et la syphilis artérielle du poumon, Arch med-chir de l'app respir, 1928, iii, 269-282.
- ¹⁶VON GLAHN, W. C., and PAPPENHEIMER, A. M. Specific lesions of peripheral blood-vessels in rheumatism, Am Jr Path 1926, ii, 235-249.
- ¹⁷PLENGE, K. Zur Frage der Syphilis der Lungenschlagader, Virchows Arch f path Anat, 1930, cclxxv, 572-584.
- ¹⁸RECKE, T. Über Syphilis der Pulmonalarterie, Centralbl f allg Path u path Anat, 1930, xlix, 257-260.

Gonococcal Endocarditis*†

Summary of the Literature and Report of a Case

By ARTHUR M. HOIRMAN, M.D., and FLOYD C. TAGGART, M.D.,
Los Angeles, California

THAYER,¹ in 1922, stated that "gonorrheal cardiac infections as a whole are by no means very unusual" In contrast to the wide prevalence of gonorrheal urethritis this cardiac complication is rare Thayer, at that time, reviewed the literature and reported seventy-two cases including twelve new ones of his own In a comprehensive survey of the literature since 1922 we can find reported only eight authentic cases, to which we add another

CASE REPORT

A white woman, aged 19, maid, was admitted to the Santa Fe Coast Lines Hospital, Los Angeles, on July 13, 1930, as convalescent from an operation for acute appendicitis The operation had been performed at Phoenix, Arizona, on July 2, 1930 She had been seized with abdominal pain, nausea, and diarrhea on July 1, 1930 Her temperature previous to operation was 101.4° F, pulse 116, respirations 22 Leucocytes were 17,950, with polymorphonuclears 89 per cent Rigidity and pain were localized to the right lower quadrant Laparotomy was performed the next morning, and an enlarged, moderately distended, hyperemic appendix was removed The pelvis was examined at the request of the patient, and a retroverted uterus, but no other pathology, found The

post-operative course was stormy, with fever to 105.4° F A blood culture was taken at this time and was reported sterile On July 12th, ten days after operation, she was transported from Phoenix to Los Angeles

Physical examination, on admission to the hospital, revealed a small, fairly well developed young female, 5 feet 4 inches tall, weighing 110 pounds Scalp, no abnormalities Eyes pupils reacted to light and distance No jaundice, strabismus or nystagmus No exophthalmos or lid-lag Conjunctivae were of fair color and free from petechiae Fundi revealed no abnormalities Nose and Ears showed no abnormalities Mouth tongue dry and coated Tonsils hypertrophied Mucous membranes injected Herpes simplex limited to the left side Neck bilaterally enlarged cervical glands No venous fillings or pulsations Thyroid not enlarged Lungs equal movement, normal resonance Breath sounds vesicular No râles Heart no demonstrable hypertrophy to percussion Rate 106, regular, P₂ greater than A₂ Blood pressure 110/70 Abdomen draining operative wound in right lower quadrant Liver and spleen not palpable No masses Extremities no clubbing, tremors or deformities There was marked hyperextension of the elbows Reflexes knee jerks, ankle jerks, biceps, triceps and abdominals, present, equal, and active Skin normal texture, somewhat pale Pelvic examination not done Urine cloudy, specific gravity 1024, acid, sugar absent, albumin trace, acetone absent, moderate number of pus cells, a few epithelial cells, no casts Blood hemoglobin 67 (Sahli), red blood cells 4,200,000, white cells 13,200, with 81

*From the Santa Fe Coast Line Hospital, Los Angeles, California

†Received for publication, August 10, 1931

per cent polymorphonuclear neutrophils, 8 per cent lymphocytes, 11 per cent large mononuclears Wassermann test negative

The temperature of 100° F on admission ranged from 98.4° to 100° F during the first ten days Drainage from the abdominal wound persisted At times, a scanty vaginal discharge was noted, and a cervical smear contained a moderate number of gram-negative intracellular diplococci, morphologically gonococci The patient developed bilateral lower abdominal pain and it was thought that a salpingitis might be present Hot vaginal douches gave relief

July 23 hemoglobin had dropped to 58 (Sahli), red count 4,020,000, white count 9,200, with 81 per cent polymorphonuclear neutrophils Temperature is recorded in chart reproduced as figure 1

A blood culture taken July 30, and planted on Swartz agar plus one-third hydrocele fluid, remained sterile Smear for malaria was negative Quinine sulphate had no effect on the fever

By August 3 the abdominal wound had stopped draining and was closing

August 5 hemoglobin was 48 (Sahli), red blood count, 3,510,000, white blood

count, 9,800 with 75.5 per cent polymorphonuclear neutrophils The red cells showed a slight degree of achromia

August 8 400 cc of whole blood was given

August 10 the genito-urinary consultant stated, "Purulent discharge from urethra Moderate cervical discharge Bartholin glands not involved Neither tube palpable No evidence of abscess Complains of some frequency and burning This is due to the urethritis Advise no local treatment until she is able to be up"

August 15 hemoglobin was 51 (Sahli), red blood count, 3,610,000, and the white blood count, 14,300, with 82 per cent polymorphonuclear neutrophils

August 26 patient was seen by one of us and the following note made "After period of fever for thirty-two days post-operative with leucocytosis, negative blood culture, no definite petechiae, clubbing, heart murmur or palpable spleen, temperature subsided for three or four days, then recurred There is a progressive secondary anemia The spleen is now definitely palpable A loud blowing systolic murmur can be heard at the apex whether due to anemia or endo-

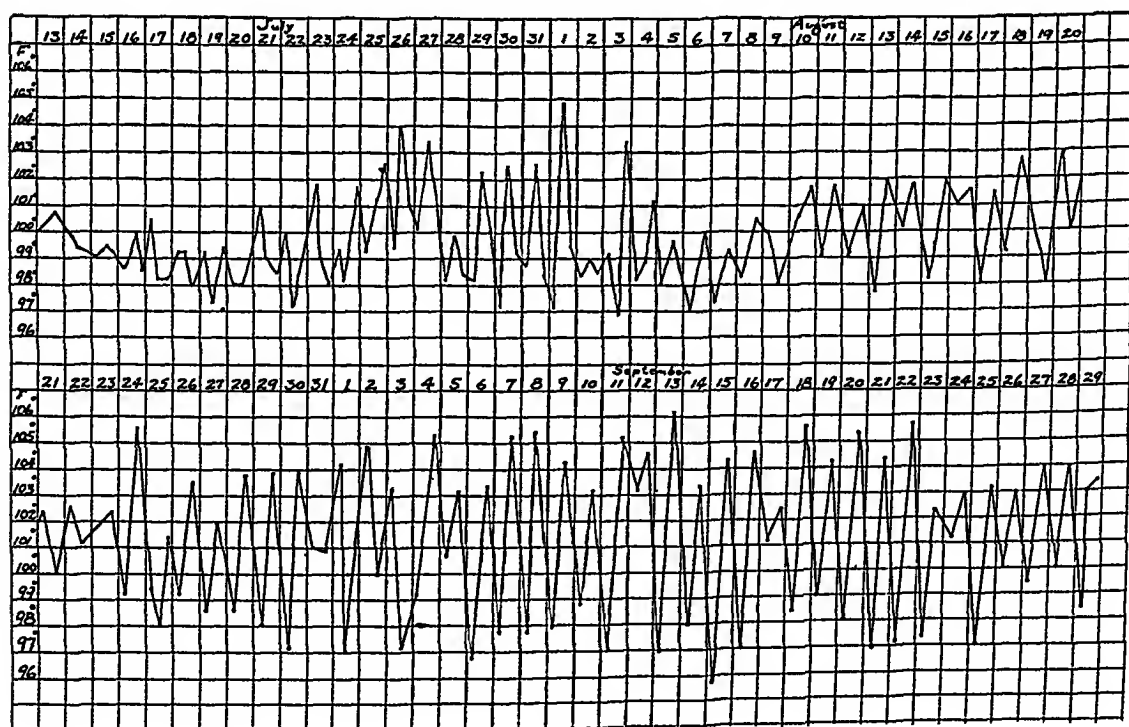


FIG 1

carditis cannot be stated. There are no visible petechiae but there is suggestive clubbing of fingers. Blood culture to be repeated for gonococci. Hemoglobin, on this date, 38 (Sahli), red blood count, 3,000,000, white blood count, 7,400, with 87.5 per cent polymorphonuclear neutrophils.

September 3 three petechial spots found on the left hand.

September 5 hemoglobin, 33 (Sahli), blood count, 2,480,000, white blood count, 5,100, with 83 per cent polymorphonuclear neutrophils.

September 6 transfusion of 350 c.c. whole blood.

September 9 laboratory reported as follows: "Blood cultures on Swartz agar plates with hydrocele fluid were sterile after seven days. Glucose broth with an equal amount of hydrocele fluid incubated four days and transplanted to Swartz hydrocele slant showed positive culture in 24 hours. Organisms were gram-negative, biscuit-shaped diplococci in pure culture. Culture positive for gonococci."

September 9 progress note by one of us: "Blood culture for gonococci finally positive on second culture. Change in heart murmur. Definite diastolic blow localized to third and fourth interspaces to left of sternum." Electrocardiogram showed sinus tachycardia. Rate 100, with upright P, T and QRS complexes in all leads. Patient was too ill to do an orthodiagram.

September 12 hemoglobin, 29 (Sahli), red blood count, 1,980,000.

September 13 transfusion 500 c.c. whole blood.

September 15 hemoglobin, 32 (Sahli), red blood cell count 2,060,000.

September 17 acriflavin hydrochloride, 0.3 gm, given intravenously. A transfusion of 500 c.c. of whole blood from a patient convalescent from gonorrheal arthritis was administered. On this date, a third blood culture was taken and was reported positive for gonococci, thus making the second positive culture.

September 19 hemoglobin, 38 (Sahli), 2,180,000, white blood count, 6,400, 83 per cent polymorphonuclear neutrophils.

September 21 acriflavin hydrochloride 0.45 gm intravenously.

September 24 "Sudden hemoptysis to-

day. Probable pulmonary infarct. Several new petechiae on anterior chest wall. One in right lower lid has disappeared."

September 26 "Condition grave. Innumerable petechiae. Marked clubbing of fingers present."

September 29 patient died.

Autopsy performed by Coroner's Surgeon John H. Schafer, September 30, 1930, was reported as follows:

"I performed an autopsy on September 30, 1930, at the Los Angeles County Coroner's Mortuary, and found the body jaundiced, graded three. There were many petechiae in the skin over almost the entire body.

"Upon opening the body, the heart was found to be about normal in size and there was a purulent pericarditis. Smears from the pericardial exudate revealed no organisms. The epicardium showed numerous petechiae and there were a few petechiae in the myocardium. The leaflets of the mitral valve were the site of large vegetations (see figure 2) and smears from these revealed large numbers of gram-negative, intracellular diplococci morphologically identical with the gonococcus. No other gross lesions of the heart were found.

"Both lungs showed an extreme degree of congestion and edema with innumerable small hemorrhagic foci, with many small pin-point abscesses in the center of the hemorrhagic foci. The hilus of the right lung showed what appeared to be a beginning infection by direct extension from the adjacent pericardium.

"The spleen weighed 800 grams, was very soft and showed many large infarcts.

"The kidneys were about normal in size and the right one showed a number of small septic infarcts.

"The liver was jaundiced, pale, and there was a fibrinopurulent deposit on the right dome.

"The intestines in the lower portion of the abdomen were covered with a light fibrinopurulent exudate and were lightly adherent. The appendix was missing. The uterus and adnexa were covered with a similar exudate and were lightly adherent to the surrounding structures. The tubes and ovaries showed no gross lesions except the exudate described. The uterus was very small, sharply anteflexed, and the cervical canal

showed the typical palmate folds of the virgin uterus. The uterus had not been pregnant. There is a history of recent positive smears for gonococci from the cervix."

Since Thayer's review of the subject of gonorrheal endocarditis in 1922, there have been in all nineteen case reports of so-called endocarditis with gonococci as the etiological agent. We say "so-called" because of the lack of absolute evidence culturally in most of these case reports. Thayer admits the necessity of positive blood culture intra-vitam, or post-mortem culture from the heart valve, for diagnosis. In the twenty cases which he reports from the Johns Hopkins Hospital records, fourteen were so proved. Six had negative blood cultures intra-vitam and only bacterioscopic evidence

of gonococci on the heart valves post-mortem. All of these cases, however, had either a specific urethritis or positive smears from the cervix uteri. They, therefore, are presumptive cases, only, probably satisfactory clinically but not bacteriologically.

We hold with Karsner² that "gonococcal endocarditis must show the presence of gonococci in the blood or lesion to be accepted as such." We would further add that the determination of gonococci from the lesion, post-mortem, is certain only by culture. Either positive intra-vitam culture or post-mortem culture from the lesion is essential to an absolute etiological diagnosis. Smears from the heart lesions without culture and with

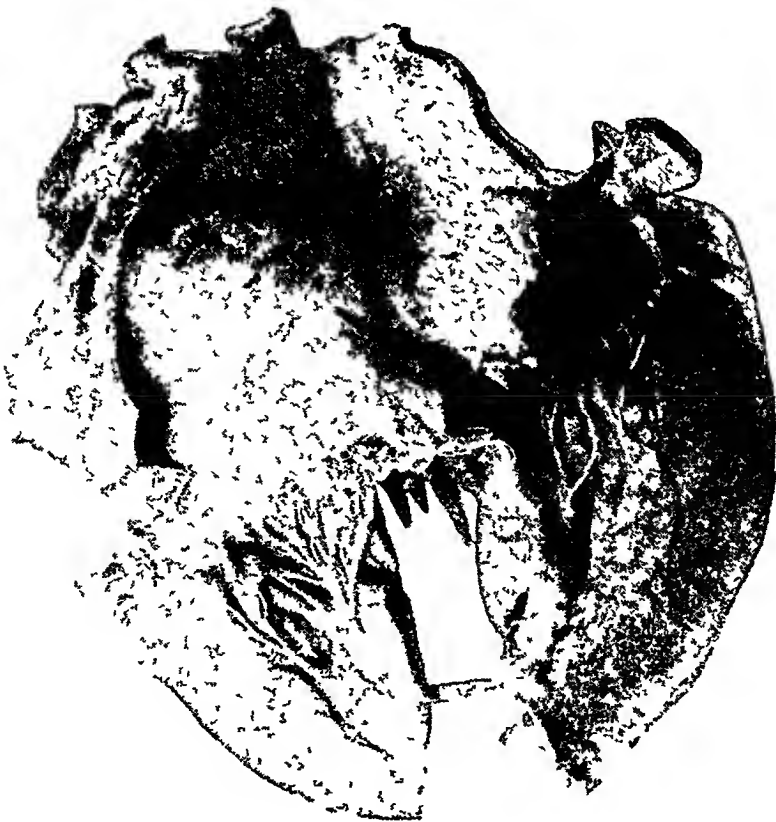


FIG 2

negative blood culture intra-vitam would be presumptive evidence only

In dealing with gram-negative diplococci, the difficulty of differentiation between gonococci and meningococci must be considered. Only within recent years have the cultural differences between these two organisms been made with any degree of certainty. This differentiation is particularly important in view of the numerous recent case reports of meningococcus septicemia with or without endocarditis, most of the cases without meningitis. On clinical grounds there seems little possibility of confusing these two types of septicemia. As stated above, Thayer's negative blood and valve culture cases all had specific urethritis or cervicitis as a point of differential diagnostic value clinically. The not infrequent association, however, of positive gonococcic urethritis or cervicitis and an endocarditis due to a secondary invading organism, as the streptococcus, staphylococcus, or pneumococcus, must be kept in mind. It is in cases of this type, with negative intra-vitam blood cultures, that the possibility of error in considering them instances of gonorrheal endocarditis arises.

Cases reported by Aubertin and Gambillard,³ Villela and Torres,⁴ Bard, Langernon and Gardère,⁵ Gallois,⁶ Edwards,⁷ Johnston and Johnston,⁸ Kramer and Smith,⁹ McCants,¹⁰ Klein,¹¹ Lion and Levy-Bruhl,¹² and Herzog and Kouzmin,¹³ all lack positive blood cultures intra-vitam or positive cultures from the post-mortem lesions. Most of them can be classed as clinically presumptive but unproved cases.

Authentic culturally proved cases

have been reported since 1922 by Gallois,⁶ Barbe and Meynet,¹⁴ Riecker,¹⁵ Brebner,¹⁶ Pratsicas,¹⁷ Vander Veer,¹⁸ Kramer and Smith,⁹ and Perry.¹⁹ These eight with our one case make only nine authentic cases since Thayer summarized the literature in 1922. The seventy-two cases which he reviewed included at least six which were presumptive only, making a total to date of only seventy-five culturally proved cases. This small number is in striking contrast to the wide prevalence of gonococcus infection. Of Thayer's reported group only five cases recovered. Since his report only one instance of recovery can be found. Repeated small transfusions seemed to be the factor of importance in the recovery in this instance. In our patient, similar transfusions were of no avail. Tabbutt²⁰ reported two instances of gonococcus septicemia with positive intra-vitam blood cultures without endocarditis, both proved at autopsy. Such findings emphasize the importance of autopsy confirmation of the presence or absence of endocarditis in the presence of culturally proved septicemia.

The value of complement fixation as a diagnostic aid in gonococcus endocarditis is questionable. Because it raises this question and also because of the relative inaccessibility of the article, we summarize the case report of Herzog and Kouzmin,¹³ of Moscow.

An adult male developed an acute urethritis on November 1, 1926. Under local treatment the discharge subsided but the patient persisted in running a temperature from 37° to 40° C for almost three months. On December 29 a blood culture was sterile. A systolic murmur developed. He suffer-

ed pain in the left kidney region, interpreted as due to an embolus. Complement fixation reaction was positive. Autopsy on February 9, 1927, demonstrated a vegetation on the mitral valve. Smears or cultures are not reported. They base their diagnosis of a gonococcic endocarditis on the presence of the urethritis, continued fever, systolic murmur, vegetation on the mitral valve, and a positive complement fixation test. In what manner the complement fixation reaction can be considered specific for gonorrheal endocarditis we do not know. It seems reasonable to presume that gonococcic urethritis alone would make it positive, and so include this case report, as one of the presumptive clinically but unproved culturally cases of gonococcal endocarditis.

SUMMARY

1 The literature on gonococcus endocarditis is summarized to date.

The eight authentic cases reported since 1922 are reviewed. To these we add another. They make a total of seventy-five proved cases of gonococcus endocarditis in the literature.

2 The criteria of diagnosis are discussed. A positive diagnosis of gonococcal endocarditis can be made in the presence of clinical evidence of endocarditis only when intra-vitam blood cultures are positive for gonococcic or when cultures from post-mortem lesions reveal the same organism.

Since the writing of this article an additional authentic case of gonococcal endocarditis, proved by postmortem culture, has been reported by H. B. Kirkland.²¹

REFERENCES

- ¹THAYER, W. S. Cardiac complications of gonorrhea, *Johns Hopkins Hosp Bull*, 1922, xxxiii, 361-372.
- Bacterial or infective endocarditis, *Edinburgh Med Jr*, 1931, New series, xxxviii, 307-331.
- ²KARSNER, H. T. Pathology of endocarditis, summary review, *Jr Am Med Assoc*, 1931, xcvi, 411-417.
- ³AUBERTIN and GAMBILLARD. Endocardite blennorragique guérie par la sérothérapie antigonococcique, *Bull. et mém Soc. méd. d'hôp. de Paris*, 1924, xlviii, 512-517.
- ⁴VILLELA, E., and TORRES, O. M. Gonococcus endocarditis, *Sciencia med*, Rio de Jan., 1924, ii, 703-709.
- ⁵BARD, LANGERNON, and GARDERE. Endocardite végétante de l'orifice pulmonaire chez un blennorragique récent atteint de néphrite aiguë, *Lyon méd*, 1925, cxxxv, 639-42.
- ⁶GALLOIS, P. M. Endocardite gonococcique, *Paris Thesis*, 1925, No 300.
- ⁷EDWARDS, B. B. Gonorrheal endocarditis, *U. S. Vet. Bur. Med. Bull*, 1929, v, 360-363.
- ⁸JOHNSTON, J. I., and JOHNSTON, J. M. Gonococcal and pneumococcal vegetative endocarditis of pulmonary valve, *Am. Jr. Med. Sci.*, 1929, clxxvii, 843-849.
- ⁹KRAMER, S. E., and SMITH, J. V. Gonorrheal septicemia and endocarditis, *Jr. Med. Soc. New Jersey*, 1930, xxvii, 311-315.
- ¹⁰MCCANTS, J. M. Gonococcus infection of heart, with report of two fatal cases due to gram-negative diplococcus, *U. S. Nav. Med. Bull*, 1930, xxviii, 603-613.
- ¹¹KLEIN, P. M. Endocardite infectieuse gonococcique, mort le 48^e jour après l'accouchement, *Bull. Soc. d'Obst. et gynéc.*, 1927, xvi, 524-526.
- ¹²LION, G., and LEVY-BRUHL, M. Un cas d'endocardite infectieuse gonococcique avec sérodiagnostic positif, *Arch. d. mal. du coeur*, 1922, xv, 289-297.
- ¹³HERZOG, A., and KOUZMIN, T. Gonorrheal endocarditis, *Vratch. d.VELO*, 1929, xii, 512-514.
- ¹⁴BARBE, E., and MEYNET, P. Une observation de septicémie gonococcique avec endocardite maligne, *Ann. d. mal. vén.*, 1922, xvii, 27-36.
- ¹⁵RIECKER, H. H. Gonococcic bacteremia with gonococcic endocarditis and aor-

- titis, *Am. Heart Jr*, 1929, i, 191-195
- ¹⁶BRENNER, I W Case of gonococcal endocarditis, *Jr Med Assoc So Africa*, 1927, i, 371-372
- ¹⁷PRATSIS, A Contributions a l'etude des manifestations viscerales de la gonococcie (endocardite, pneumonie), *Paris med*, 1928, lxxvii, 521-528
- ¹⁸VANDER VEE, J N Pure gonococcal endocarditis, with death, *Urol and Cut Rev*, 1929, xxiii, 815-817
- ¹⁹PERRY, M W Gonorrheal endocarditis with recovery, case report, *Am Jr Med Sci*, 1930, clxxix, 599-605
- ²⁰TABBUTT, A H Gonococcal septicaemia, *Med Jr Australia*, 1926, ii, 451-452
- ²¹KIRKLAND, H B Gonococcus endocarditis, *Am Heart Jr*, 1932, vii, 360-369

The Value of Knowledge of Personality

“FORECASTING the future of body-minded man, and not a decapitated being, is an interesting and, on certain occasions, a wise precautionary measure. We should not, however, allow our forecasting proclivities to divert attention, as so frequently happens today, from the importance of acquainting ourselves with the knowledge that can be readily obtained from reviewing the data supplied by heredity, environment, physical characteristics, the nature of the emotional and mental reactions, the habits of life, the tendencies to face or dodge reality, academic tests, estimates of intelligence, and information bearing on the social environment and the reactions of the individual to the people with whom he is brought into contact. Without this information we can only try in a very bungling manner to direct the expenditure of human energy. Unless we have definite information in regard to the individual personality, we can only expect to make ridiculous attempts to fit young people for school, college, business, industry or life. Without this information we should not expect to be much more successful than we are at present in fitting children into home surroundings, struggling students into academic environments, apprentices into their trades, business men into bigger business enterprises, and misfits of various kinds into society.

(From *Prohibiting Minds and the Present Social and Economic Crisis*, by STEWART PATON, M D, Paul B Hoeber, Inc, New York City)

The Significance of Lymphatic Tissue and Adenoma-Like Areas in the Thyroid Gland* ** †

By L. R. HIMMELBERGER, Ph D, *Flint, Michigan*

WHILE the terms Graves' disease, Basedow's disease and exophthalmic goiter are purely clinical expressions and their use in pathological connections perhaps questionable, no suitable pathological term exists that is descriptive of the changes seen in the thyroid gland in this disease. Parenchymatous hypertrophy and hyperplasia have been used quite properly but these expressions do not describe the most important changes seen, as we hope to show. The present clinical tendency to consider "toxic adenoma" as a condition separate from Graves' or Basedow's disease also lends confusion to a pathological understanding of the process in the thyroid gland.

The association of thyroid disease with a general lymphadenopathy and the idea that in some way or other it was related to changes in the thymus is by no means a recent conception, for as early as 1905 Hansemann¹ reported four cases of Basedow's disease coming to necropsy in which a general lymphatic hyperplasia was observed.

*From the Laboratory of Hurley Hospital, Flint, Michigan

**Thesis presented to the Faculty of Michigan State College, in partial fulfillment of the requirements for the degree of Doctor of Philosophy

†Received for publication, April 15, 1931

At that time he suggested a relationship between thyroid and "status lymphaticus". In 1908 Capelle² also took a similar attitude and in 1911, with Bayer,³ reported beneficial results from thymectomies on Basedow patients. Bircher,⁴ in 1912, reported experiments in which he produced Basedowian symptoms in dogs by implantations of thymus glands from patients suffering from thyroid disease. Pettavel⁵ wrote on the pathological anatomy of Basedow's disease in four well studied cases. In two cases he found a persistent thymus, in all he found areas of lymphoid tissue in the thyroid gland, and in three there existed a general hyperplasia of the lymphatic tissue throughout the body. He failed, however, to place diagnostic significance on the lymphoid hyperplasia in the thyroid. Matti⁶ reported necropsies on ten cases in which general lymphoid hyperplasia was a striking feature. In but one case did he fail to find lymphoid follicles in the thyroid. This patient was a twelve year old child however, and one may properly question the existence of Graves' disease. Rautmann,⁷ also studying the pathological anatomy, demonstrated a general lymphadenopathy with lymphocytic infiltration in the thyroid. Pettavel⁸ reported addi-

tional work in 1914, and Klose,⁹ in 1916, also called attention to the general lymphoid hyperplasia existing in thyroid disease

In this country many writers have mentioned the presence of pseudo-nodes, lymphatic tissue, round cell infiltration, etc, in the thyroid gland McCallum's¹⁰ is the only text book on General Pathology which refers to these areas He says that definite lymphoid nodules are found in exophthalmic goiter and but rarely if ever found in normal glands He fails however to ascribe any significance to their presence Aschoff,¹¹ while lecturing in this country, spoke of the presence of pseudo-nodes in both Basedowian and non-Basedowian glands, and observed that they are more frequently found in glands from Basedow patients Sager¹² mentioned the presence of lymphocytes, but evidently did not consider them of significance Rienhoff¹³ gave them a place in the pathological picture of thyroid disease, but evidently did not consider them to be of diagnostic importance Broders¹⁴ has always considered them to be evidence of thyroiditis Menne, Joyce and Von Hungen¹ also believed them to be of inflammatory origin Warthin¹⁵ was the first in this country to point out the pathological significance of areas of lymphatic hyperplasia He alone at that time (1924) considered rudimentary lymphoid areas as being of diagnostic importance, thus definitely suggesting a new diagnostic criterion in Graves' disease, the essential pathological changes of which have been considered, for nearly 40 years, to rest exclusively in the acinar epithelium

and amount of contained colloid It was Warthin's observations that first engaged the writer's interest and stimulated the study in this laboratory Elovzin¹⁷ working here in 1927 made a limited study of our material then available It was Warthin's contention in 1924 and again in 1929 that the presence of lymph tissue was diagnostic of potential Graves' disease or exophthalmic goiter He gave further impetus to the idea held by the previously quoted continental observers that this tissue indicates a definite pathological constitution, the so-called thymico-lymphatic type of individual, or as he preferred to call it, the "Graves' constitution" He pointed out that these individuals present a hyperplasia of the lymphoid tissue throughout the body and took the position that they have a congenital predisposition to Graves' disease In a recent survey of one hundred and eighty-one post-operative cases, Clarke and Black¹⁸ also concluded that a constitutional factor is involved Simpson¹⁹ supports this view in a study of 665 resected thyroids On the other hand, Hellwig²⁰ in a recent article opposed Warthin's views, basing his conclusions on a study of fifty-eight surgical and seven postmortem specimens He concluded that the presence of lymphocytes in the thyroid is the result of a simple local reaction to hyperactivity of the gland, that they are of no diagnostic importance and can in no way be interpreted as evidence of a so-called Graves' constitution Sixty-six per cent of his cases presented lymphocytic infiltration and he cites a group of cases without clinical symptoms in which these areas were present in

38.5 per cent. He does not state the reasons or indications for the surgery in this latter group. One is led to believe that he assumes lymphocytic infiltration to be present in 38.5 per cent of normal glands.

It is the purpose of this paper to present an interpretation of the significance of lymphatic tissue in the thyroid gland as gained from a study of material collected over a period of six years, consisting of (1) thyroids from stillborn infants, premature births, and very young children coming to necropsy, (2) surgically resected thyroid glands and, (3) necropsy material from older subjects who died from conditions not in any way involving the thyroid gland, together with observations on the so-called adenomata of the thyroid.

If Warthin's thesis is tenable, that there exists a definite type of individual possessing a "Graves' constitution," who is potentially a case of exophthalmic goiter, that constitution must be congenital and the significant lymphatic areas should be present at birth or even in uterine life. A routine search of thyroids of young subjects should, therefore, be rewarded with a certain percentage incidence of the lesion. Material for this section of the study consists of thyroids from 140 full term, premature and still-born infants. Further, if the lesion under consideration is a part of the "Graves' constitution", and is of diagnostic significance, it should be present in all cases of true Graves' disease and it should be capable of demonstration in practically all resected glands from such cases. This material consists of three hundred and eighty-six glands

removed surgically. Still another point of proof susceptible to demonstration rests in a study of supposedly normal glands obtained at necropsy.

According to Warthin's thesis not all of those individuals possessing this "Graves' constitution" develop clinical Graves' disease. It should, therefore, be possible to show a small incidence of the lesion in question in postmortem material from subjects devoid of thyroid history. While this incidence should be less, it should be roughly comparable with that found to be existent in the glands of infants, prematures, etc. Our material studied in this connection consists of glands from two hundred cases selected from the standpoint of a nonthyroid history.

The normal thyroid has been quite intensively studied by many workers. No attempt will be made here to present a review of this literature. Suffice it to say, that in all the literature consulted, no mention is made of the presence of lymphatic tissue in the normal thyroid except by Marine,²¹ who said merely that lymphocytes do occur normally. He dismissed the subject with a single sentence and failed to state the extent to which it was observed.

Williamson and Pearce²² in an extensive study of the normal gland made no mention of lymphoid tissue. Rienhof,²³ working with serial sections and using reconstruction methods, said nothing of their presence in normal glands. In view of the fact that lymphoid areas failed to attract the attention of most investigators of the normal gland, one may feel safe in assuming that such tissue is not a com-

mon histological component of the normal thyroid

STUDY OF INFANT THYROIDS

This material, as before stated, was secured from premature fetuses, still-born infants, and infants that lived but a short time after birth. Most of the material came from still-born infants, but we have several specimens from fetuses as young as the fifth month of gestation. In passing, it is perhaps of interest to note that colloid was present in the acini of these fetal thyroids to a greater or less degree. This is in keeping with the observation of Murray¹ and others quoted by him. A search of the literature reveals few studies of fetal or infant glands, Murray makes no mention of lymphocytes, neither does he speak of adenomata. Rautmann, however, did observe small areas of lymphocytes in rare instances while studying glands from very young children. Warthin also mentioned their occurrence in rare instances. Our study of glands from these cases was confined to a search of microscopic preparations for areas of lymphocytes and to observations on the presence of adenomatous areas.

The histological picture of the thyroid gland from the young subject is quite constant. Maturity of the epithelial cells lining the acini is apparently established prior to birth and colloid storage is a pre-natal function of the gland, at least as early as the fifth month. Murray has shown that post-mortem desquamation of acinar epithelium is responsible for the appearance of acini filled with epithelial cells. This is also our experience. Study of microscopical sections from one hundred and forty glands from

the sources above outlined revealed the presence of lymphoid areas in four cases only. Two of these were still-born infants, one was a baby three weeks old, dying from hemorrhagic disease of the new-born, while the other was an infant that lived for but a few hours after birth, death being due to cerebral hemorrhage. These results give a percentage incidence of the lesion of approximately 2.8 per cent. Had more material been available a more accurate incidence would of course have been established, as it is very obvious that in a matter involving low percentages a large mass of material is quite essential. These results, however are indicative of findings that could confidently be expected in a large number of cases. A further consideration of this percentage incidence will be taken up in connection with postmortem material from older subjects. There was one case in which the lymphoid bodies were found which was not included in the series because of the other pathology present. This was a case of a child nine months old, dying a so-called thymic death. This case was previously reported by the writer²⁵ and the observation made at that time was that no areas of rudimentary lymphoid tissue were found in the thyroid parenchyma. During the progress of this work a re-study of this case was made, new sections were cut and an intensive search revealed the presence of lymphoid areas. This experience points out the necessity of numerous blocks and careful search.

Of the one hundred and forty specimens examined, areas of so-called "fetal" adenoma were observed in three cases. These areas are separ-

ated from the adjacent parenchyma by a thin fibrous connective tissue capsule and there is a definite difference in the appearance of the cellular structure. Little or no colloid is seen in these areas, the cells are very compact, and take a much deeper nuclear stain.

RESECTED THYROID GLANDS

In a study of surgical material, the conclusions at which one may arrive are made difficult by the perplexing question of the clinical diagnosis as recorded on the patient's chart and because of the paucity of the clinical information, for it is upon these clinical records that the comparative study must be based. With the aid of experienced clinicians we have attempted to classify our material into two groups (1) those cases showing undoubted clinical evidence of Graves' disease and (2) those cases in which the data in the record did not warrant such a conclusion, or cases which were definitely diagnosed as not of a Graves' character. The criteria used for the first group were Tachycardia, exophthalmos, tremor, increased pulse pressure, definite loss of weight and increased basal metabolic rate. Cases showing any three of the above clinical symptoms were considered, perhaps liberally, as true Graves' disease. All others were placed in the second group. It is very obvious that errors in classification are certain to occur inasmuch as the information in some instances was meagre and incomplete, not representing, perhaps, a true picture of all the clinical signs present.

Slides from 386 surgical cases were studied with the following histological findings

Lymphatic tissue with no epithelial hypertrophy	123
Hypertrophy of epithelium with lymphatic tissue	62
Hypertrophy of epithelium with no lymphatic tissue	4
Hypertrophy, lymphatic tissue and adenoma	12
Lymphatic tissue and adenoma	59
Adenoma, iodization and degeneration	7
Colloid gland only	45
Cystic degeneration without hypertrophy or lymphatic tissue	28
Iodism	46
	<hr/> 386

Examination of the tabulated observations, shows the presence of lymphoid tissue in 246 cases, while epithelial hypertrophy existed in but 68 cases. There were four cases showing epithelial hypertrophy without lymphatic areas. These cases were among our earliest material and but few blocks were available in each case. We feel that had sufficient material been available the lesion could have been demonstrated in these cases. The low incidence of epithelial hypertrophy is in striking contrast to the high incidence of lymphoid areas and represents a valuable feature in the study of these glands. Were epithelial hypertrophy the only pathological change considered as indicative of Graves' disease, a marked difference between clinical and pathological findings would exist, since of the 246 cases showing rudimentary lymphoid tissue, all but eleven had been diagnosed, or showed definite clinical signs of, Graves' disease, as did the four cases showing epithelial hypertrophy only. The eleven cases not classified as clin-

ical Graves' disease were cases with a very meagre history in each instance, with the clinical diagnosis given as "toxic goiter", which would perhaps warrant their classification as Graves' disease since, clinically, this term is often used interchangeably with Graves' disease. Of the other 140 cases, nine had been classified according to our standards as clinical Graves' disease. The fact that these failed to show lesions of the disease is, we feel, due to our liberal clinical requirements or to having "missed" the areas because of an insufficient number of blocks having been taken. Two of these cases were classed pathologically as undergoing degeneration, four as iodism, while in three no definite changes could be detected. The data presented emphasizes the importance of recognizing the presence of lymphoid tissue and its interpretation as a pathological feature of Graves' disease, since practically all cases showing the classical clinical signs of the Graves' syndrome present the lesion in question.

Those glands classified as adenomatous all contained encapsulated areas of atypical thyroid tissue in different stages of development, but no case showing adenomata as the only deviation from normal presented true clinical signs of Graves' disease. The clinical adenoma described by clinicians is not, in our opinion, an adenomatous structure at all but merely represents a nodular portion of the thyroid containing perhaps large amounts of hypertrophic tissue. We have observed in a few cases that the areas of lymphoid tissue are more numerous in these nodular structures than in tissue taken at some distance from the

nodular portions. We feel that this accounts for the so-called "toxic adenoma" and the prevailing impression that removal of the "adenoma" gives clinically beneficial results. That there is some doubt as to the permanency of these beneficial results is shown by the recent survey of Clarke and Black.¹⁸

There were twenty-eight cases of large glands showing no evidence of Graves' disease. These all showed, grossly, areas of degeneration of various degrees, some adenomatous, but consisting for the most part of colloid cysts containing old hemorrhage and softened tissue. A few were undergoing calcareous degeneration and an occasional one showed definite necrosis. It is possible that tissue dissolution products in these degenerated glands may supply a toxic amount of the thyroid hormone and thereby cause symptoms that clinically simulate the Graves' syndrome, thus being responsible for many diagnostic errors. This point seems susceptible to experimental study and experiments embracing it are now in progress.

The forty-six cases reported as iodism demand consideration since the question of iodine-Basedow which formerly occupied a large place in the literature is now receiving but scant attention. According to Crotti,²⁸ individual sensitivity to iodine varies widely. Many patients tolerate large amounts of iodine, while in others, very small amounts are responsible for marked disturbances. Moreover, some of those who have previously shown good tolerance to iodine preparations suddenly develop pronounced symptoms of iodine-Basedow. In this day of iodine salt (particularly in

Michigan) and proprietary reducing nostrums containing iodine, when practically everyone is receiving iodine constantly or at intervals, it seems to us that the question is deserving of more consideration than ever. Warthin contended that over-iodization will produce clinical signs simulating Graves' disease. Jackson²⁷ also writes of a type of hyperthyroidism being caused by iodine. In one of our cases diagnosed clinically as Graves' disease by the physician, and having a basal rate of $+30$, together with a mild tachycardia and slight loss of weight, we failed to find lymphoid areas. Upon investigation it was found that this patient had previously been using proprietary goiter remedies containing iodine, and had been further iodized by his physician. Histologically, the tissue presented all of the involutional changes described as due to iodination.

Warthin reported in 1924 an analysis of 976 resected glands. Of these, 247 presented areas of lymphatic tissue while 154 showed both lymphatic tissue and epithelial hypertrophy. A large portion of Warthin's material was collected before the extensive use of iodine as a preoperative therapeutic procedure which no doubt accounts for the greater incidence of hypertrophic epithelium as compared to our results in this connection. The remainder of the cases studied by Warthin showed no evidence of Graves' disease and the physical findings did not warrant such a diagnosis.

The absence of epithelial hypertrophy in a large proportion of the specimens is no doubt due to epithelial involution due to iodine therapy. Many observers including Sager, Rienhoff

and Warthin have pointed out the involutional effects of iodine in exophthalmic goiter. At the present time practically all cases of Graves' disease coming to surgery are iodized preoperatively, consequently a non-treated surgical specimen is rare indeed. Rienhoff, in particular, studied the effect of iodine on the involution of thyroid epithelium in exophthalmic goiter. His observations were made upon seven well considered cases in which artificial involution was studied at various stages. He describes the changes due to iodine as follows:

- "(a) Increased amount and density of colloid
- (b) Increase in size and regularity of acini
- (c) Increase in amount of connective tissue in the septum and scarring throughout the gland
- (d) Decrease in size and height and change in shape of epithelial cells from a high columnar to a cuboidal or endothelial cell
- (e) Decrease in cytoplasmic bodies or constituents
- (f) Decrease in vascularity of gland
- (g) Decrease in vacuolization of colloid and deposits of lymphocytes"

Warthin believed that overiodination produces a "watery" colloid and that lymphocytic exhaustion of the germ centers of the lymphoid tissue results. In our experience extensive iodination also causes marked atrophy of the epithelial cells lining the acini, the cytoplasm is decreased and the nucleus contracted and deformed. We have been unable to show a definite difference in the lymphoid areas in overiodized and underiodized specimens because of our inability to surmount the difficulty of obtaining specimens from the same patient before and after iodination.

SELECTED POSTMORTEM THYROIDS

In a study of the thyroids from 1000 autopsies Warthin found 32 showing areas of lymphoid tissue. Two of these were also carcinomatous. These findings give a 3.2 per cent incidence of lymphoid areas in a routine examination of all cases coming to necropsy. These cases were evidently not selected with reference to the exclusion of thyroid involvement and possibly included some cases which had previously suffered from Graves' disease.

As before stated we studied slides from 200 cases without thyroid involvement, many of them in the younger age groups (early part of first decade). In this study we made the following observations:

Epithelial hypertrophy	0
Lymphatic tissue	4
Areas of adenomatosis	9

The percentage incidence of lymph tissue was 2 per cent. While this is considerably lower than Warthin's figures it corresponds to the incidence of these areas found in infant glands, since theoretically the incidence should be higher in the case of the latter. It will be seen that the incidence of adenoma-like areas in selected necropsy and infant material is also within comparable limits.

ADENOMA

A study of this surgical material has made possible observations regarding adenoma. Many clinicians consider toxic adenoma a disease independent of Graves' disease, but as before stated, the clinical term "adenoma" has no reference to histology and is applied to nodular forms of thyroids which may not be involved in Graves' disease. Reinhoff from his series of seven care-

fully studied cases of exophthalmic goiter in which involution was established by the administration of iodine, came to the conclusion that a large proportion of those areas considered adenomata are but residual areas of hypertrophy and hyperplasia which have remained refractive to iodine or because of disturbed vascular supply have not been subjected to its influence. Ewing's miliary adenomata were considered by him to be such areas. He offered as a possible explanation for the failure to secure permanent remission from iodine the suggestion that these areas of persistent hypertrophy maintain a state of hyperthyroidism. Warthin considered the adenoma of the thyroid as a congenital anomaly due to altered vascular supply and therefore altered development results. Ewing considered the fetal adenoma as being embryonal. Menne, *et al*, considered adenoma as a separate division in their system of classification.

Our observations have disclosed the following facts:

1 Small areas of adenoma-like structures are capable of demonstration in certain slides from infant thyroids. These areas present a cell arrangement distinct from the balance of the tissue.

2 Adenomatous areas, both the so-called "fetal" and mature types, are seen in postmortem material from selected non-thyroid cases.

3 These adenomatous structures are quite as frequently found in non-toxic glands as in so-called toxic cases. Figure 1 shows a gross specimen of adenoma and figure 2 shows an area of lymphocytes in the thyroid tissue outside the encapsulated area at "A."

4 A study of 100 glands from



FIG 1 Gross specimen of thyroid with adenoma, to show area from which figure 2 was made

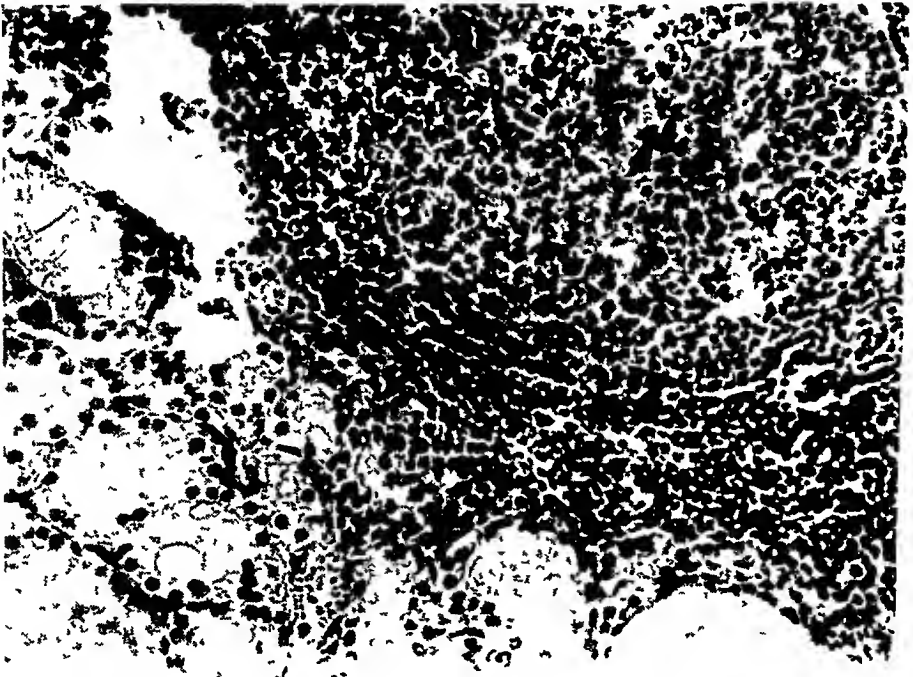


FIG 2 Photomicrograph showing an area of lymphocytes in the non-adenomatous tissue at 'A' in figure 1

dogs of all ages and breeds shows the presence of these adenomata in a small percentage of the glands

In view of the foregoing it appears to us that "fetal adenoma" bears no relation to thyroid disease. We have no cases of adenoma in our material which presented clinical signs of toxicity that were not shown to be Graves' disease, as determined by the presence of lymphoid tissue. The presence of these areas of adenoma-like structure in infant glands would tend to refute the conclusions of Rienhoff that they are persistent hypertrophic areas. Their presence in postmortem material of all ages, as well as in infants lends support to the view of Warthin that they are congenital structures. Their presence in dog thyroids leads to a safe assumption that they are in no way related to Graves' disease, *per se*, as dogs are supposedly not subject to the Graves' syndrome.

COMMENT

In this study of the occurrence of rudimentary lymphoid tissue and exophthalmic goiter we have included limited observations on the significance of adenomatous areas. The data presented from the examination of infant and selected necropsy material may be taken together when considering Warthin's hypothesis that these pseudonodules are evidence of constitutional deviations from normal. The presence of areas of lymphatic tissue in infant glands is perhaps of greater significance than their presence in the glands from necropsies of older subjects, inasmuch as one is not confronted by the question of pre-existing Graves' disease, although we have tried to obviate this factor in the selection of

our necropsy cases. We were unable to follow Warthin's study with reference to a general lymphoid involvement in exophthalmic goiter for the reason that but one necropsy case of exophthalmic goiter was available. In this one case, a female 50 years of age, cervical and mediastinal lymph nodes were enlarged and hyperplastic, the thymus was mildly persistent having a weight of 6 grams and the liver showed marked degenerative change. Menne *et al* take the position that lymphocytes in the thyroid gland are the result of inflammatory absorption reactions following sustained hyperactivity of the gland and that the "prolonged activity probably leads to the necessity for more supportive stroma." While there might be some defense for this reasoning regarding the presence of this lesion in adult thyroids, it is hardly conceivable that this explanation would hold in cases of infant glands. Furthermore, a considerable number of our specimens came from children succumbing to so-called "summer diarrhea" and it is interesting to note that none of these showed the presence of these areas. It would be a conceivable possibility that were they the result of a true inflammatory process, one would be able to demonstrate their presence in an infectious disease of this type in which there is a marked disturbance of all metabolism, and in which a general lymphadenosis exists. Numerous other childhood diseases were represented in our material and in no case were these areas of lymphoid tissue noted. In a case of miliary tuberculosis in a child 8 months of age, diligent search of many sections failed to disclose the presence of lymphoid areas in the face of the presence of a distinctly local

infectious process of acknowledged chronic type

Another case in point is our failure to find these areas after exhaustive search of many sections in a necropsy case of generalized tuberculosis in an adult even though a definite tuberculous process was demonstrated in the thyroid. Hellwig also believes that lymphocytic infiltration is the result of a purely local response, inflammatory in nature, but the number of his cases is small and he offers no assurance of exhaustive search for areas of lymphoid tissue. We have repeatedly called attention to the necessity of many blocks and intense study. We feel that the discrepancies occurring in our work are largely due to this factor. Figure 3 shows a small area of lymphoid tissue in a gland with extensive epithelial hypertrophy in all sections. This was the only area of lymphatic

tissue found, however, in sections from many blocks. Furthermore, it is not our experience that with these areas epithelial hypertrophy always co-exists. We have seen many cases in which no epithelial hypertrophy and but an occasional area of lymphoid tissue could be demonstrated in sections from many blocks. In one instance only a single area of lymphoid tissue was found in sections from nine different blocks, none of which showed hypertrophy of the epithelium. We fully agree with Warthin that epithelial hypertrophy persists longer in and about the lymphoid tissue in the face of iodination and feel that this is the proper interpretation when the two processes are found to be co-existent. These observations, in our opinion, indicate that the production of rudimentary lymph nodes does not form a part of the picture in inflammatory processes in



FIG 3 Photomicrograph showing the only area of lymphoid tissue found in numerous sections from a gland showing extensive epithelial hypertrophy

the thyroid gland and that the lesion in question is not of inflammatory origin

The almost universal presence of this lesion in surgical thyroids from patients exhibiting clinical Graves' disease is the main point of interest in the entire work, since Warthin's interpretation of lymphocytic areas as a diagnostic criterion is strongly supported. To us, there is a difference in the amount of lymphatic tissue and the degree of its hyperplasia, depending on the severity of the toxic symptoms of the patient and the degree of clinical response to iodine treatment. Figure 4 is a photomicrograph of a specimen from a patient whose basal metabolic rate, before iodine treatment was $+43$, improvement under iodine was very slight, the basal rate remained high and partial resection of the gland was of but slight clinical benefit. Later

a nearly total extirpation was considered necessary. The microscopical picture of the two specimens of thyroid gland were essentially identical, though nearly two months elapsed between the two resections. Lymphatic nodules were numerous throughout all sections and epithelial hypertrophy is persistent, particularly adjacent to the lymphatic tissue. On the other hand figure 5 is from a case with a few symptoms, basal rate of $+21$, and showing microscopically but an occasional area of lymphatic tissue, though many blocks were examined. While we have several such comparative instances we realize that definite conclusions would necessitate a painstaking study of a great number of cases with carefully taken histories. We have also observed that in those cases of infant and selected necropsy glands showing lymphatic tissue, definite



FIG 4 The marked development of lymphoid tissue in the thyroid of a severe case of exophthalmic goiter

hyperplasia is lacking, the tissue not showing very distinct germ centers (Figure 6) Continuing this line of reasoning it would follow that symptoms of Graves' disease manifest themselves only when these congenital areas become hyperplastic and further, that the more extensive the hyperplasia the more severe are the symptoms As said before it is our observation, as well as Sager's, that these areas persist in the face of evident adequate iodine therapy We do not know, however, that they are not reduced in number, size and degree of hyperplasia Rein-hoff, who has studied glands before and after involution makes the statement that "The areas of lymphocytosis were much less frequent during and after involution and the areas that were present seemed to be markedly reduced in size" One must recall however, that this observation is based upon seven specimens only

The futility of too enthusiastic generalization on so limited a number of cases is too obvious to require comment Warthin also considers them to be affected when iodine treatment is first instituted, but that they later become increased in size From this, one might be led to conclude that the transitory or partial benefit derived from iodine is in halting further hyperplastic processes in the lymphoid tissue as well as in the epithelial elements of the gland We have previously called attention to the fact that the use of iodine as a therapeutic agent oftentimes so changes the appearance of the gland of exophthalmic goiter as to make the recognition of a definite pathological process next to impossible were one to consider the epithelial elements only While there is no question in our mind regarding the definite pathology exhibited by the thyroid epithelium, we are forced by our own

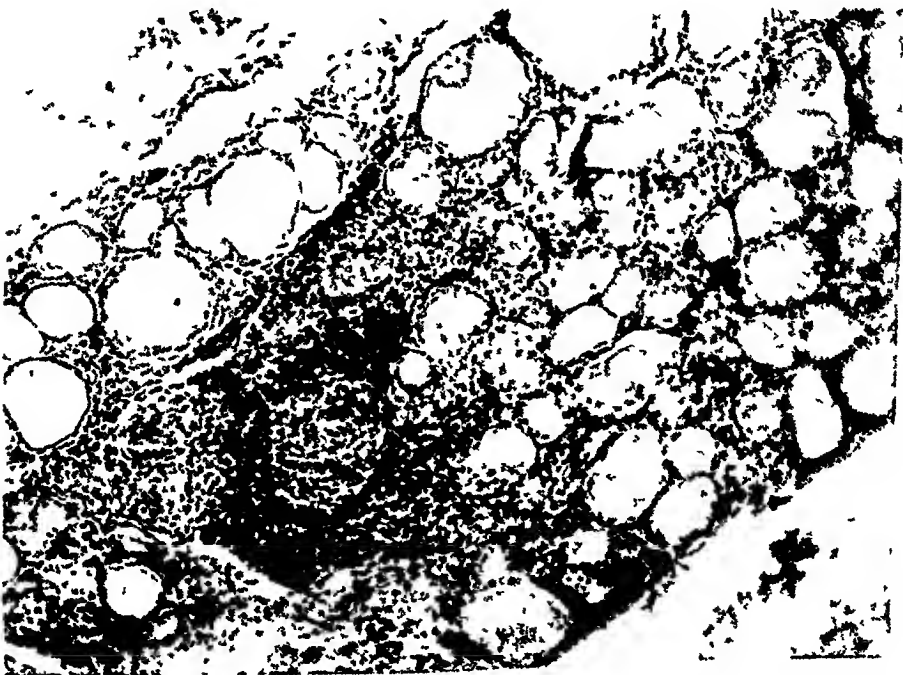


FIG. 5. Lymphoid tissue in a mild case of exophthalmic goiter

experience as well as by the evidence presented in the literature, to recognize its instability as a pathognomic lesion of Graves' disease in the presence of iodine treatment

We have shown a remarkably close agreement in the clinical diagnosis and the pathological picture when the presence of lymphatic tissue was considered an essential lesion of Graves' disease. Were this lesion to be ignored and the conclusions drawn only from the epithelial hyperplasia and hypertrophy exhibited, a regrettably poor agreement between clinical and pathological findings would result. The presence of lymphatic tissue in practically all glands removed surgically from patients exhibiting undoubted clinical signs of the Graves' syndrome, forces one to consider it a lesion of this disease. We feel that the few cases in which the lesion was not demonstrated represent clinical diagnostic errors or

cases in which the lesion was missed because of insufficient search. In this respect this lesion can be compared to infiltrating malignant cells in the prostate, for instance, where it is oftentimes necessary to section many blocks before carcinomatous areas can be found. Certainly, failure to demonstrate these areas of lymphatic tissue in a few blocks does not warrant a conclusion that they are not present in other portions of the gland. Their persistence after iodine medication confers upon them a major role as a diagnostic lesion inasmuch as we have shown them to be a much more trustworthy indication of hypertrophic and hyperplastic processes than changes in the epithelium.

In the course of a study such as this, one is impressed by the futility of attempting the solution of many of the questions involved by drawing conclusions from a study of dead pathol-

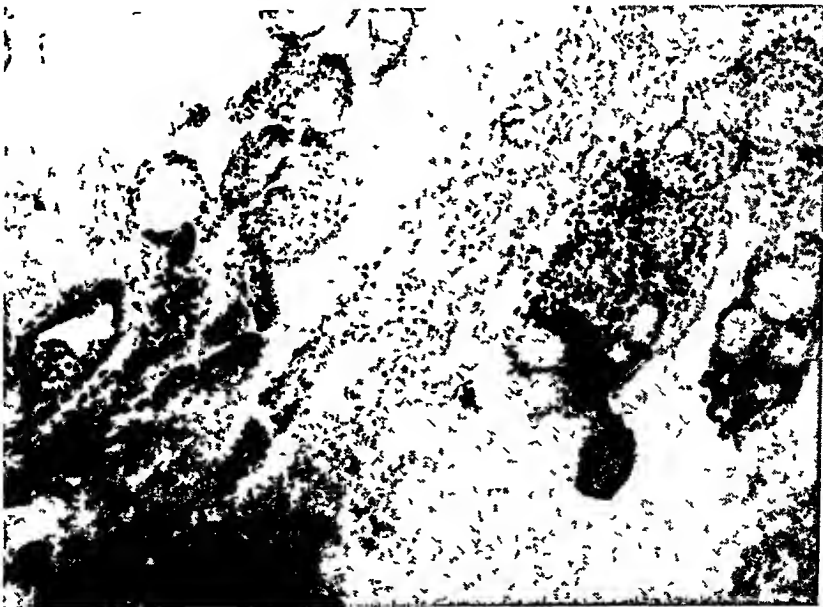


FIG 6 A small area of lymphoid tissue in the thyroid gland of an infant

ogy The problems involved, which are necessary of solution for a clear understanding of thyroid disease, must, in our opinion, be attacked by experimental methods for any reasonable hope of success. Such methods are yet to be devised.

CLASSIFICATION OF THYROID DISEASE

There are many classifications of thyroid disease suggested in the literature, few of which permit both clinical and pathological application. Menne *et al* have proposed perhaps the most extensive workable classification, although it does not coincide with our view that there exists but one process involved in hyperthyroidism, that symbolized by the clinical syndrome of Graves' disease. Warthin proposed a simple classification as follows:

- 1 Simple colloid goiter without Graves' constitution,
- 2 Nodular colloid goiter without Graves' constitution,
- 3 Simple adenoma with Graves' constitution,
- 4 Exophthalmic goiter (Graves' constitution),
- 5 Adenoma with Graves' constitution (so-called toxic adenoma)."

This classification is applicable clinically and is based on the presence or absence of the "Graves' constitution." It recognizes and emphasizes the adenomata in a manner that is to us confusing and not warranted, since it is our contention that the presence of adenomatous areas has no significance in hyperthyroidism. As has been often stated, no classification of any disease is of value that cannot be of clinical as well as pathological application. If the symptoms exhibited by the patient, be they ascribed to Graves' disease, hyperthyroidism, toxic adenoma, or

what not, fit a given syndrome, and there is a constant pathological lesion, one is warranted in assuming the unity of the process. In view of the findings in our study, the practically universal presence of the lesion described as lymphoid hyperplasia, we suggest the following classification and diagnostic scheme:

- 1 Hypertrophic-lymphoid goiter—Graves' disease
 - 1 Epithelial hypertrophy in non-iodized gland
 - 2 Lymphoid hyperplasia
 - 3 If iodized
 - 1 Stroma increased
 - 2 Colloid increased, thin and watery
 - 3 Epithelial hypertrophy may be patchy or lacking
- 2 Nodular colloid goiter
 - 1 Large vesicles containing colloid occurring in pseudo-encapsulated areas
 - 2 No lymphoid tissue or epithelial hypertrophy
 - 3 May show degenerating colloid cysts
- 3 Simple colloid goiter
 - 1 Large vesicles, comparatively uniform
 - 2 No lymphoid tissue or epithelial hypertrophy
 - 3 May show degeneration, cysts, calcification
- 4 Normal thyroid with adenomata
 - 1 Encapsulated areas of "fetal"-like acini or
 - 2 Areas of more developed adenoma
- 5 Inflammatory processes
 - 1 Definite pyogenic infections
 - 2 Tuberculosis, etc
- 6 Malignant new growths

If any thyroid would otherwise fall in the last five groups it will be seen that the presence of lymphoid tissue necessitates placing it in group 1. All the groups become modified by iodination and all may contain adenomatous areas, and in addition there will be the rare specimen usually obtained at necropsy from the potential Graves' patient which will present small areas of lymphoid tissue. These latter cases must necessarily be considered as potential exophthalmic goiter in the absence of clinical signs.

CONCLUSIONS

1 It has been shown that areas of lymphatic tissue occur in the thyroid gland in 28 per cent of infants.

2 This tissue is also found in 2 per cent of thyroids from patients dying from diseases or accidents not involving the thyroid gland.

3 Areas of lymphatic tissue occur in practically all thyroid glands re-

moved surgically from cases of undoubted Graves' disease.

4 The lesion described is not the result of a local inflammatory reaction.

5 The presence of lymphatic tissue in infant and selected necropsy specimens supports Warthin's contention of the existence of a "Graves' constitution", that exophthalmic goiter is the clinical manifestation of a congenital constitutional anomaly.

6 Warthin's conclusion that this lesion is diagnostic for Graves' disease is vigorously supported.

7 Adenomata have no causal relationship to the symptoms of thyroid disease since they occur with equal frequency in normal and pathological glands. The use of the term should be abandoned in connection with the clinical diagnosis of hyperthyroidism.

8 A simple classification and diagnostic scheme of thyroid disease that is clinically and pathologically compatible is suggested.

REFERENCES

- ¹HANSEMAN, D. Schilddrüse und Thymus bei der Basedow'schen Krankheit, *Berl klin Wchnschr*, 1905, xlii, No 44a, 65-66.
- ²CAPELLE, Beziehungen des Thymus zum Morbus Basedowii, *Deutsch med Wchnschr*, 1911, xxxvii, 1771.
Über die Beziehungen der Thymus zum Morbus Basedow, *Bruns' Beiträge zur klin Chir*, 1908, lviii, 353-393.
- ³CAPELLE, W., und BAYER, R. Thymektomie bei Morbus Basedow. Ein Beitrag für die Beziehungen der Thymus zur Basedow'schen Krankheit, *Bruns' Beiträge zur klin Chir*, 1911, lxi, 214-238.
- ⁴BIRCHER, E. Zur experimentellen Erzeugung des Morbus Basedowii, *Zentralbl f Chir*, 1912, xxxix, 138-140.
- ⁵PERTAVEL, C. A. Beitrag zum pathologischen Anatomie des Morbus Basedowii, *Deutsch Ztschr f Chir*, 1912, cxvi, 488-542.
- Weiterer Beitrag zur pathologischen Anatomie des Morbus Basedowii, *Mitt a d Grenzgeb d Med u Chir*, 1914, xxvii, 693-749.
- ⁶MATTI, H. Die Beziehungen der Thymus zum Morbus Basedowii, *Berl klin Wchnschr*, 1914, li, No 28, 1310-1316, No 29, 1365-1370.
Über die Kombination von Morbus Basedowii mit Thymushyperplasie, *Deutsch Ztschr f Chir*, 1912, cxvi, 1165-1167.
- ⁷RAUTMANN, H. Pathologisch-anatomische Untersuchungen über die Basedow'sche Krankheit, *Mitt. a d Grenzgeb d Med u Chir*, 1915, xxviii, 489-618.
- ⁸PERTAVEL, C. A. Weiterer Beitrag zur pathologischen Anatomie des Morbus Basedowii, *Mitt a d Grenzgeb d Med u Chir*, 1914, xxvii, 693-749.
- ⁹KLOSE, H. Die pathologisch-anatomischen Grundlagen der Basedow'schen Krank-

- heit, Beitr z klin Chir, 1916, cii, 1-109
- ¹⁰MCCALLUM, W G A textbook of pathology, 1928, W B Saunders Co, Philadelphia
 - ¹¹ASCHOFF, S Lectures on pathology, 1924, Paul B Hoeber, New York
 - ¹²SAGER, W W Exophthalmic goiter, pathologic change as a result of the administration of iodine (Lugol's solution), Arch Surg, 1927, xv, No 6, 878-894
 - ¹³RIENHOFF, W F Involutional or regressive changes in the thyroid gland in cases of exophthalmic goiter, and their relation to origin of certain of the so-called adenomas, Arch Surg, 1926, xiii, 391-425
 - ¹⁴BRODERS Personal communication
 - ¹⁵MENNE, F B, JOYCE, T M, and VON HUNGEN, A P Thyroid disturbances, clinicopathologic study of three hundred instances, Arch Surg, 1926, xiii, No 3, 329-342
 - ¹⁶WARTHIN, A S The constitutional entity of exophthalmic goiter and the so-called toxic adenoma, Ann Int Med, 1928, ii, 553-570
Pathology of goiter, Proc Inter-state Post Grad Med Assoc, N Am, (1929), 1930, v 383-385
 - ¹⁷ELOVZIN, M Concerning presence of lymphocytes in thyroid gland, Jr Detroit Coll Med and Surg, 1930, i, 72-82
 - ¹⁸CLARKE, N E, and BLACK, I Postoperative results in toxic goiter, Arch Int Med, 1930, xlv, 266-282
 - ¹⁹SIMPSON, W M Graves' constitution (Warthin), Am Jr, Surg, 1929, New series vii, No 1, 22-26
 - ²⁰HEILWIG, C A Graves' constitution (Warthin), Surg Gynec and Obst, 1931, lii, 43-51
 - ²¹MARINE, D The thyroid, parathyroids and thymus, special cytology, (E V Cowdry), 1928, i, 549-620, Paul B Hoeber, New York
 - ²²WILLIAMSON, G S, and PEARCE, I H The structure of the thyroid organ in man, Jr Path and Bact, 1923, xxvi, 459-469
 - ²³RIENHOFF, W F Gross and microscopic structure of the thyroid gland in man, Arch Surg, 1929, xix, 986-1036
 - ²⁴MURRAY, I M The thyroid gland in the full-term foetus and in the newly born infant, Brit Med Jr, 1927, i, 5-8
 - ²⁵HIMMELBERGER, L R Status lymphaticus,, Jr Mich Med Soc, 1928, xxvii, 337-339
 - ²⁶CROTTI, A Thyroid and thymus, 1922, Lea and Febiger, Philadelphia
 - ²⁷JACKSON, S S Iodine as a cause of hyperthyroidism, Jr -Lan, 1924, xlv, 324-328
 - ²⁸EWING, J Neoplastic diseases, 1928, W B Saunders Co, Philadelphia

Pulmonary Lesions in Human Tularemia*†

Pathologic Review and Report of a Fatal Case

By STANLEY D. BLACKFORD, M.D., *University, Virginia*

ALTHOUGH it is well known that tularemia is a blood-borne infection, little notice has been taken of the frequency with which it attacks the lung. Francis¹ reported abstracts of the twenty-four fatal human cases of which he had record up to October, 1928, and in more than one-third of these a diagnosis of intercurrent bronchopneumonia had been made. Simpson² subsequently expressed the opinion that the physical signs in many of these so-called bronchopneumonias were probably due to multiple tularemic necroses. The author³ has recently published the thirteen cases which have come under his personal observation and six of these gave clinical evidence of intrathoracic disease (i.e. pleural effusion, 2, bronchopneumonia, 2, bronchitis, 1, lung abscess, 1).

It seems more than a coincidence that each of the eight cases in which the chest was examined at necropsy should have shown some abnormality of the lungs or pleura. Death in these occurred from four days to five months after the tularemic infection. Simpson² reported "two lesions in the right lung, which were unquestionably

tularemic focal necroses." Palmer and Hansmann⁴ found "an inconsiderable amount of bronchopneumonia which did not give any clinical symptoms." Bardon and Berdez⁵ reproduced a photograph showing tularemic nodules on the visceral pleura of their case and said "both lungs showed an extensive bronchopneumonia." Bunker and Smith⁶ removed twenty-eight ounces of a deep straw colored fluid from the right thorax at necropsy and made a diagnosis of "coagulative necrosis of the right lung." Goodpasture and House⁷ withdrew 200 c.c. of fluid from the left chest postmortem but were unable to find evidence of intrapulmonary damage. Verbrycke's case⁸ had about 100 c.c. of fluid in each pleural space and "multiple areas of caseous necrosis averaging a hickory nut in size" in the lungs. Francis and Callender⁹ quoted a case of Bruecken's dying five months after infection, in which "a calcareous area at the left apex was traced to a multilocular single cavity one centimeter in diameter."

In February, 1931, Masee¹⁰ reported finding physical signs of pneumonia at the bases of both lungs in a case of tularemia dying on the eighteenth day of the disease. At necropsy, gross examination revealed areas of "late red hepatization" in both lungs which were

*From the Department of Internal Medicine, University of Virginia Hospital.

†Received from publication, August 3, 1931.

interpreted as representing a "bronchopneumonia of the confluent type". Numerous short gram-negative bacilli, morphologically consistent with *B. tularensis*, were seen imbedded in the tissue sections. Material from the lung was scratched into the skin of the abdomen of a guinea pig, a granulomatous ulcer developed from which *B. tularensis* was cultured. This case shows that bronchopneumonia may be a manifestation of tularemia rather than a complication of it.

Many writers have remarked on the great similarity of the microscopic pictures seen in the tubercle of tuberculosis and in the caseous necrosis of tularemia, although the comparison has been made mostly in tissues other than the lung. Since the fundamental lesion in both is initially a small area of caseation, this resemblance is not remarkable. It seems peculiar that so little attention has been paid to the similarity of the clinical effects which may be produced by *B. tuberculosis* and *B. tularensis*. Bronchopneumonia, pleural effusion, lung cavitation and lung abscess formation are at least some of the clinical conditions which may be caused by both organisms. One wonders if perhaps a few cases of tularemia have not been mistakenly diagnosed as tuberculosis.

Reference to the microscopic pulmonary lesions in human tularemia are scarce. Simpson¹¹ in his recent monograph on the disease discusses this phase briefly: "Foci of caseous necrosis with peripheral epithelioid and fibroblastic proliferations also characterize the hepatic and pulmonary lesions." Stitt¹² paraphrases Francis' description as follows: "The lungs present small necrotic foci or white plaques on

the pleura, they contain focal necroses, or there may be bronchopneumonia of any degree, even to the involvement of almost an entire lobe, the alveolar walls are infiltrated with edema and large mononuclears, and the alveolar contents consist of a few leucocytes and red blood cells and a small amount of fibrin." At this time, the criteria for making the diagnosis of tularemia of the lung from pathologic studies alone seem indefinite. Further work is necessary along this line.

The following case is presented because few fatal cases of tularemia have been reported. The pulmonary lesions described are sufficiently similar microscopically to the other cases reported to deduce that the changes in the lungs in this case were due to tularemia. It is felt, however, that they are also sufficiently different to be of especial interest.

REPORT OF CASE

History A negro, aged 38, was sent to the hospital on Dec 6, 1928, from Culpeper, Va. At the time of admission the patient gave an unreliable history but the following facts were supplied by his family physician, Dr J. W. Humphries.

On Nov 4, 1928, the patient, who had had no contact with rabbits during the preceding six months, skinned an opossum found dead in a cage with several live opossums. Four days later his physician was called because of the sudden onset of chills, fever, generalized aching and prostration. The temperature was 102° F. It was observed that the patient's hands "were considerably chapped" although no ulceration was noted. On Nov 11, when the physician called again, the temperature was 103° F and "a suppurative condition around four badly broken front teeth had developed." There was swelling of the glands of the neck. On Nov 16, at the advice of his physician, two of these teeth were extracted under local anesthesia and a "large amount of pus was evacuated." The patient was

able to sit up during the following twenty-four hours, but, on Nov 17, was again forced to bed. On this date, a specimen of blood was sent to the Virginia State Board of Health Laboratory for Widal agglutination and was reported negative. In accordance with their custom of testing all Widal-negative serums with *B abortus* and *B tularensis*, these additional agglutinations were done. The *B abortus* agglutination was negative but the agglutination with *B tularensis* was reported "positive in dilution of 1:40". The agglutination was repeated with a specimen of serum obtained on Dec 3 and was positive with *B tularensis*, 1:5120. The same serum tested by the U. S. Hygienic Laboratory agglutinated in dilution of 1:1280.

On Dec 6, the patient was admitted to the hospital, mainly on account of cough which had developed about two weeks previously. The cough was productive of abundant foul, bloody sputum and was becoming progressively worse.

Examination. The patient was emaciated, obviously ill, sweating profusely, and apparently in stupor. There were many carious teeth with marked pyorrhea and receding gums, and cavities of the two recent extractions. The left axillary glands were slightly enlarged but not tender. The other glands were normal. In spite of a careful search, no ulceration of the skin and no scars were found. There was an old crushed fingernail on the left third finger. The physical signs in the chest indicated fluid or consolidation, or both, in the right lower lobe. Routine examination was otherwise normal. Rectal temperature was 105° F, pulse 120, respiration 32. The blood pressure was 128 systolic, 84 diastolic. Urinalysis was essentially negative. Hemoglobin was 53 per cent (Dare), red blood cells numbered 2,710,000, white blood cells 8,200. The blood smear was typical of secondary anemia and the differential count was 79 per cent polymorphonuclears, 21 per cent lymphocytes. The serum agglutinated *B tularensis* strongly in dilutions of 1:800 and gave an incomplete reaction in dilution of 1:1600. It did not agglutinate *B typhosus* or *B abortus*. The blood Wassermann reaction was negative. The sputum was composed of reddish-brown, bloody, mucopurulent material, no

acid fast or Vincent's organisms were found in six examinations.

Course. The patient remained toxic and at times irrational. His temperature was of the septic type, ranging from normal to 105° F. He coughed up foul bloody sputum, filling one or two sputum cups a day. On Dec 8, an attempt at thoracentesis was unsuccessful. On the 10th, a single bedside chest plate (figure 1) was reported as follows: "The lower half of the right chest shows a marked increase in density which is honeycombed with large irregular areas of decreased density, these have fairly definite borders. The largest of these areas of rarefaction is 6 by 3 cm and occupies the space between the sternal ends of the second and fourth ribs. The appearance on the left is that of rather heavy hilus shadows. This region is also thickly studded with small round areas of calcium deposit."

Conclusions. Lung abscesses, right, probable bronchiectasis, left. The patient continued to become more toxic and died from general toxemia on Dec 15, 1928.

Necropsy. Examination was performed three hours after death by Drs. Harry T. Marshall and Joseph B. Graham.

The pleural cavities contained no fluid. The anterior aspect of the right lung was normal. The middle lobe was adherent to the upper lobe and partially so to the lower. Posteriorly the lung was bound down by extensive and firm adhesions at the base. On removing the right lung a cavity was encountered where the lung had been attached. This cavity was 8 by 12 cm and extended from the diaphragm to within a centimeter of the top of the lower lobe. It seemed as if the anterior wall was formed by rough, irregular, dirty gray, necrotic lung tissue, and the posterior wall by the visceral pleura which was adherent to the chest wall. This cavity contained about a pint of foul, purulent, bloody fluid. A probe passed down the main bronchus failed to communicate with this cavity. On section a large friable thrombus was found almost obstructing the lumen of the right pulmonary artery, numerous thrombosed arterioles were seen.

The left lung was congested in spots but elsewhere was pale. It was somewhat emphysematous. A slightly darker region occurred in the upper lobe, the pleura was lit-

tle involved over this area. A thrombus was found partially filling the pulmonary artery at the hilus. The outer wall of the thrombus was more pliable and the center was softer than in the right lung. Section through the consolidated area showed multiple thrombi.

In the angle of the bifurcation of the trachea there was a walnut sized mass of lymph nodes, which were coherent, soft and under tension. On section, there was much pigment deposit and three or four very small pearly spots which did not project above the surface.

The pericardium and heart appeared grossly normal except for a cloudy swelling of the myocardium. Both the spleen and liver failed to reveal any lesions suggestive of tularemia either on the surface or on section. The liver was of the fatty, nutmeg variety and the spleen resembled an acute splenic tumor of the septicemic type. The kidneys were cloudy and congested. The other viscera were normal.

Histologic Study The microscopic sections were studied by Dr. Thelma Brumfield, who had at her disposal material loaned by Dr. Edward Francis from two of the cases reported by Francis and Callender. After a comparison of these with those from

this case, Dr. Brumfield felt justified in saying that the lesions in this case were due to tularemia. The significant features were found in the sections from the axillary and bronchial lymph nodes, the lungs and the liver. Dr. Brumfield's reports on these are quoted in detail.

"Left Axillary Lymph Node" In this section were two small areas with a central coagulative necrosis, surrounded by large mononuclear epithelioid cells and a zone of fibroblasts. No Langhans cells were seen but these two areas closely resembled tubercles. The germinal centers from other areas of this node were pale and the sinusoids contained numerous large mononuclear cells. Eosinophils were relatively abundant. Another section contained no necrotic areas and no other unusual changes except hyaline degeneration of small blood vessels.

"Hilus Lymph Nodes" There were three areas of coagulative necrosis similar to those already described except that they lacked such definite zones of epithelioid and fibroblastic cells. The other lymph nodes examined were apparently normal.

"Right Lung" One section revealed in a medium sized artery an occluding thrombus containing many clearly outlined red blood cells. This appeared to be a propagated



FIG 1 Retouched bedside film taken December 10, 1928, showing cavities in right lung

thrombus though it seemed to be partially attached to the vessel wall. In the adventitial tissue surrounding, there was a striking accumulation of mononuclear cells and a proliferation of fibroblasts in which were a few well preserved polymorphonuclear cells. The smaller vessels of this area were congested with red blood cells. Just outside the adventitial tissue the alveoli contained many large mononuclear cells. In this area there were a few spaces containing semincretic exudate, composed chiefly of mononuclear cells and some polymorphonuclears. The remainder of this section showed a diffuse widespread necrosis of the lung tissue. This resembled closely a caseous pneumonia, since within the necrotic alveolar exudate were still retained the outlines of large mononuclear cells without pus formation, and only a moderate degree of hemorrhage. Gram-Weigert stain was negative for organisms in this tissue. Another section, adjacent to the large abscess cavity, contained a few air-bearing alveoli with thickened walls, and numerous microscopic nodules of consolidated lung tissue, the centers of which were necrotic, resembling early tubercles and surrounded by epithelioid cells and collagen fibers. In the same section was an area of profuse hemorrhage into the lung tissue in which appeared numerous areas of coagulative necrosis. Histologic details here were obscured by the hemorrhage. Gram-Weigert stain was negative.

"Other sections from the wall of the abscess showed marked proliferation of fibro-

blasts with collagen production, thick walled vessels, and an exudate of mononuclear and polymorphonuclear cells. Several small arteries revealed a proliferative endarteritis.

"Two minute areas of necrosis surrounded by large mononuclear cells were seen in the sections from the liver."

SUMMARY

The reported effects of *B. tularensis* on the human lung are reviewed and attention is called to the probable frequency and importance of these pulmonary manifestations. A case with necropsy is presented with the following observations of interest: (a) the probable source of infection was an opossum, (b) the clinical diagnosis of pyogenic lung abscess was discredited by microscopic study of the tissue, (c) the pulmonary damage was extensive and of prime importance as a cause of death, (d) the multiple pulmonic thrombi, with attending areas of necrosis were probably attributable to the tularemic infection, and (e) gross caseous nodules were lacking in the liver and spleen.

Two additional reports^(13, 14) of pulmonary lesions in human tularemia have appeared since this paper was written.

REFERENCES

- ¹FRANCIS, E. Symptoms, diagnosis and pathology of tularemia, Jr Am Med Assoc, 1928, xci, 1155-1161.
- ²SIMPSON, W. M. Tularemia, study of a rapidly fatal case (four days, seven hours), Arch Path, 1928, vi, 553-574.
- ³BLACKFORD, S. D. Tularemia in differential diagnosis, Va Med Monthly, 1931, lviii, 10-13.
- ⁴PALMER, H. D., and HANSMANN, G. H. Tularemia, report of a fulminating case with necropsy, Jr Am Med Assoc, 1928, xci, 236-239.
- ⁵BARDON, R., and BERDEZ, G. Tularemia, report of a fatal case with postmortem observations, Jr Am Med Assoc, 1928, xc, 1369-1371.
- ⁶BUNKER, C. W. O., and SMITH, E. E. Tularemia, report of four cases, one fatal, with autopsy report, U S Nav Med Bull, 1928, xxvi, No 4, 901-911.
- ⁷GOODPASTURE, E. W., and HOUSE, S. J. The pathologic anatomy of tularemia in man, Am. Jr Path, 1928, iv, 213-226.
- ⁸VERBRYCKE, J. R. Tularemia, with report of a fatal case simulating cholangitis, with postmortem report, Jr Am Med Assoc, 1924, lxxxii, 1577-1581.
- ⁹FRANCIS, E., and CALLENDER, G. R. Tularemia, the microscopic changes of

- the lesions in man, Arch. Path and Lab
Med, 1927, iii, 577-607
- ¹⁰MASSELL, J C 'Tularemia in Georgia,
report of a fatal case, Jr Med Assoc.
Ga, 1931, xx, 66-67
- ¹¹STRIPSON, W M. 'Tularemia, history,
pathology, diagnosis and treatment,
1929, Paul B Hoeber, New York, p 106
- ¹²STRY, E R 'The diagnostics and treat-
ment of tropical diseases, 1929, Blakis-
ton's Son & Co, Philadelphia, Pa, p
279
- ¹³FOULGER, M, GLAZIER, A M, FOSHAY, L
'Tularemia, Jr Am Med Assoc, 1932,
cxviii, 951-954
- ¹⁴PRIMAR, H H, MACLACHLAN, W W G
'Tularemia pneumonia, Ann Int Med,
1931, v 687-698

Oliver Goldsmith, M.D.*

By LOUIS H. RONDIS, M.D., Lieutenant Commander, Medical Corps,
U S Navy

WITH no other medical poet is the dignified doctoral prefix more commonly employed. He was "Dr Goldsmith" to Boswell and the Johnson circle, and his contemporaries almost without exception referred to him as the "Doctor" yet the medical side of Goldsmith's life has been rather neglected, though it is both a considerable and interesting subject. The circumstances of his medical education, his attempts to practice in Southwark and in London, his relation to one of the celebrated nostrums of the day, and its use in his last illness are all well attested though not commonly known facts.

His biographers are unable to decide with certainty whether Oliver Goldsmith was born in the village of Pallas or the village of Elphin, Roscommon, Ireland. The year of his birth is also in doubt, though it was probably 1728. This is the date inscribed in the tablet in Westminster Abbey. Curiously enough the day of his birth, November 10, is the best authenticated of these three facts regarding the place and time of his appearance in the world. His father, the Reverend Charles Goldsmith, was a poor country curate. His son has immortalized his kindly

and guileless character in the "Vicar of Wakefield" and he was also the original of the clergyman of the "Deserted Village", "passing rich on forty pounds a year".

When Oliver was seven years of age his father's circumstances were improved by the gift of the living at Kilkenny West, and the family moved to the parsonage on the outskirts of the pretty little village of Lissoy not far from Athlone. Lissoy is celebrated as the "Sweet Auburn, loveliest village of the plain" and its rural beauties are pictured in the opening lines of the "Deserted Village".

Goldsmith attended the school at Lissoy kept by an old pensioned soldier, full of stories of Marlborough's wars and the whimsical legends of Celtic Ireland. He must have influenced the imaginative mind of the boy destined to be one of the greatest of English poets. There was little in Oliver's appearance however to indicate a brilliant future. He was homely to the point of positive ugliness, awkward, loose jointed and undersized. Smallpox, from which no one before the time of Jenner escaped, had further disfigured his countenance. A peculiar guilelessness and simplicity of character was an additional incitement to making him the target for all sorts of ridicule.

* Received for publication, October 12, 1931

At seventeen he was packed off to Trinity College, Dublin, where he was entered as a sizar or poor student. On one side of the entrance gate fronting on College Green, Trinity has erected a noble statue to this poor sizar who was to be considered by the world as one of her most famous sons, no small distinction as Trinity was also the Alma Mater of Edmund Burke, Dean Swift, Bishop Berkeley, and Thomas Moore.

Goldsmith's college career was rather stormy. He was one of those good hearted, good natured, heedless persons, easily led, and loving gayety and conviviality. Once he was expelled for participating in a riotous party within the precincts of the college. His scholarship, too, does not seem to have been very remarkable but he was finally graduated on February 27, 1749, O S, with the degree of Bachelor of Arts. The next three or four years were spent in fixing upon a profession. He attempted to take holy orders but was rejected by the Bishop, some say because of failure to pass the requisite examination, others because he presented himself to the Bishop arrayed in scarlet breeches. It was decided that he should study law and he was equipped with a new outfit of clothes, a good horse and thirty pounds. In a few months he returned with a single rusty suit, a broken down pony, and one shilling. He now lived for a time with his indulgent uncle Contarine, and made good progress in learning to play the flute and fiddle and in writing verses, accomplishments that pleased his uncle and a pretty cousin, but did not help him in securing an honorable or independent position in the world.

Most of the Goldsmith family were

poor and improvident. There was one notable exception. This was Dean Goldsmith who was the incumbent of a rich deanery and whose position and material wealth made him an oracle to his poor relatives. He appears to have asked "Why not make Oliver a physician?"

The suggestion of a great man like the Dean could not be disregarded and in the Autumn, of 1752, Oliver was entered at the University of Edinburgh as a "Student in Physic" to use his own words. As a medical student he had an experience in respect to his first boarding house that all other indigent medical students will appreciate. The table was furnished like that of Don Quixote, whose weekly menu consisted of "Soup composed of somewhat more mutton than beef, the fragments served up cold on most nights, lentils on Fridays, stew on Saturdays, and a pigeon by way of addition on Sundays." The similarity of this diet to that of Goldsmith's boarding house is shown by his description of what could be done to extend a loin of mutton throughout the week. "A brandered chop was served up one day, a fried steak another, collops with onion sauce a third, and so on until the fleshy parts were quite consumed when finally a dish of broth was manufactured from the bones on the seventh day, and the landlady rested from her labors."

He spent two winters in Edinburgh where he made a better reputation as a story teller and good fellow than as a student. However, he took a particular interest in chemistry and had for his professor, Joseph Black, the discoverer of carbonic acid gas, who remembered Goldsmith as a promising pupil. Another of his teachers was

Alexander Monro, senior, the celebrated anatomist

Goldsmith's fondness for dress and his vanity have been frequently noted. A tailor's account, while he was a medical student, is full of rich colors and fabrics. "To 2½ yds Sky-Blew satin, at twelve shillings a yard, To ¾ yds fine Sky-Blew Shalloon, 1 s yd, To a fine small hat 14 s, To 1 oz 6¼ dr silver hat lace, 8 s, to a pair fine thd black hose, to 3½ yds best fine

high claret colored cloth, 19 s" So Goldsmith was not illly dressed during this period and furthermore the tailor's ledgers show that he paid his bill.

Although the University of Edinburgh was, and is today, one of the most famous medical schools of the world Goldsmith quitted it after two years to make a tour of the Continent. In a letter to his good natured uncle Contarine, who financed him to some



FIG 1 Oliver Goldsmith, M D

degree in his medical studies, he says "I intend to visit Paris where the great Monceau instructs his pupils in all the branches of medicine and the next winter go to Leyden. The great Albinus is still alive there and 'twill be proper to go through only to have it said that we have studied in so famous a University."

Goldsmith's real reason for going abroad was no doubt his desire to see the Continent. Edinburgh was scarcely less celebrated as a medical school than Leyden, yet he well describes the advantages that take the student to another country to carry on the same studies as at home. To be able to say that one has been at a famous foreign University, the professional contacts in other lands and cities, the experiences of travel are valuable acquisitions not to be obtained in any other way, and the world takes note of these things and the returning student finds that he has an added prestige not possessed by the stay-at-home classmate.

In February, 1754, Goldsmith took up his studies at Leyden and no doubt attended the lectures of Albinus, one of the greatest of anatomists and professor at Leyden for more than fifty years. It is pretty evident, however, from certain descriptions he has given of the fair sex both at home and abroad that his studies were not all of a professional character. In one of his letters to his uncle Contarine he compares the Dutch and Scottish types of femininity. "The Dutch woman and a Scotch will bear comparison. The one is pale and fat, the other lean and ruddy, the one walks as if she were straddling after a go-cart, and the other takes too masculine a stride. I shall

not endeavor however to deprive either country of its share of beauty."

He had arrived in Holland with 33 pounds sterling and borrowed money from another Irish student, Ellis, afterwards a physician of some note, when he left Leyden and began his travels through France, Switzerland, and Italy. According to his own account much of the journey was on foot and he often stayed at the houses of peasants, paying for food and lodging by playing the flute or telling amusing stories of his adventures. The journey was begun in 1758 and lasted about one year. During it he visited Louvain, Paris, and Padua. It was from the University of Louvain that he is supposed to have received the degree of Bachelor of Medicine, a title first used in connection with his name in 1763, when it is appended to one of the Dodsley agreements. Many of the records of Louvain University were destroyed during the French Revolution so that documentary evidence was not available when Prior and Washington Irving attempted to examine into this subject. Macauley expresses his doubts that Goldsmith ever obtained a medical degree, and indeed intimates that, like all travelers, he drew the long bow pretty generally. Goldsmith himself tells of having seen Voltaire in Paris and describes a conversation with him in most circumstantial terms, though it is now known that Voltaire was not at the time within a hundred leagues of Paris so that Macauley's doubts are not ill founded. Though the question of the medical degree from Louvain cannot be settled other than by a Scotch verdict of "not proved", the general use of the title of "Doctor", Goldsmith's use of the term "Bachelor

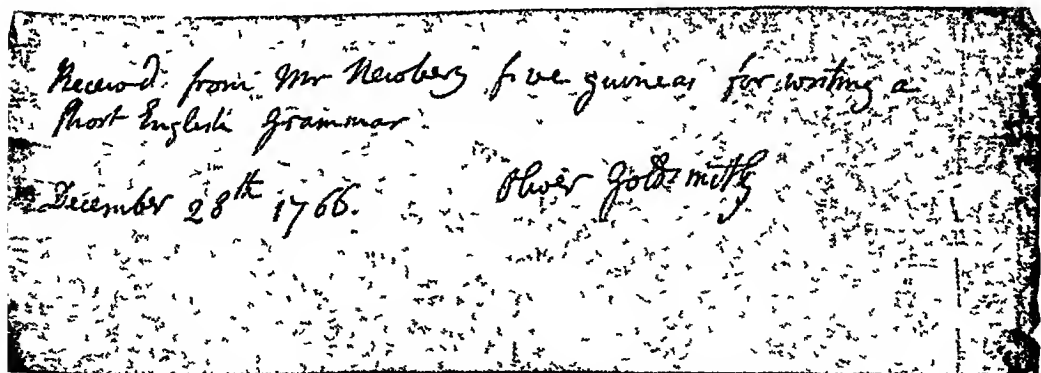
of Medicine", and his claim that this degree was received from Louvain must carry weight

Goldsmith returned to England in 1756, penniless and friendless. His uncle Contarine, who had been his patron and who had interested himself in his nephew's behalf on all occasions, was dead. For a time his circumstances were desperate. He slept in the streets and consorted with beggars. He attempted unsuccessfully to obtain employment in an apothecary shop. He did however obtain a place as usher in a private school but left it to become the assistant of a chemist. There, through the assistance of a fellow student at Edinburgh, Dr Sleight, he commenced the practice of medicine at Bankside, Southwark. He starved here, too, though he told another old college companion, Beatty, who met him at this time, that "He was practising Physic and doing well". Dr Farr, who had also been with him as a medical student, says that when he met Goldsmith at this time the poet was clothed in a coat of rusty black velvet with a patch over the left breast, an evidence of poverty that he concealed by holding his three-cornered hat over it.

Dr Sleight introduced Goldsmith to Richardson, the novelist and bookseller, who gave him some literary hack work to do and it was thus that he began his career as a man of letters. His work soon attracted the attention of Dr Samuel Johnson and through his friendship Goldsmith became a member of the famous literary club, the record of whose meetings has been so completely reported by Boswell. It is of interest that two of the original members of the club were medical men for, in addition to Goldsmith, the membership included Dr Nugent, the father-in-law of Edmund Burke, a Roman Catholic, and a successful and highly respected physician.

Both Johnson and Sir Joshua Reynolds recognized Goldsmith's genius. Hawkins says that he was looked at askance by some of the other members "as a mere literary drudge equal to the tasks of compiling and translating but little capable of original and still less of practical composition".

This view was changed by the publication of "The Traveler" and the "Vicar of Wakefield". The former has been declared with good reason to be the finest poem in English since the appearance of Pope's "Essay on Man".



Received from Mr Newbery five guineas for writing a
Short English Grammar
December 28th 1766. Oliver Goldsmith

FIG 2 An autograph receipt by Oliver Goldsmith, M.D

and the excellence of the "Vicar of Wakefield" has been attested by successive generations of readers

The years that followed were probably the most successful and happy of Goldsmith's life. He enjoyed the praise of "The Traveler" and the "Vicar", and the admiration excited by "The Deserted Village", perhaps the finest pastoral poem in English. These years also saw his success as a playwright with the comedies of "She Stoops To Conquer" and "The Good Natured Man"

He was frequently the guest of Reynolds, Mrs. Thrale and Mrs. Vesey. The given name of Mrs. Vesey's husband was Agronisham and we can gain some idea of the fame of the Johnson circle at this time when we find that Agronisham Vesey, though wealthy and socially prominent, was so concerned over his entrance into the Literary Club that the night his name came up for discussion he had a relay of foot messengers to bring the news of his election and was much agitated until he found that he had been accepted for membership. At Sir Joshua Reynolds's, Goldsmith met the Hornecks and fell in love with the younger daughter celebrated as the "Jessamy Bride". His financial affairs, though always in a tangled state due to his improvidence, were nevertheless better than at any other time in his career and he appears to have enjoyed an income of four or five hundred pounds a year. This is the time of the "bloom-colored coat" mentioned by Boswell.

Three features of Goldsmith's medical life should be noted. The first of these was his attempt to gain a medical appointment in India. This attempt was successful and he was appointed

physician and surgeon to one of the factories of the East India Company on the Coromandel Coast. The appointment was worth fifteen hundred pounds a year, a very large sum for those days, partly in salary and partly in fees and perquisites. It was necessary that he pass a professional examination and make a deposit toward his passage money before he was finally accepted for the post. He probably failed in one of these requirements for he was never actually appointed and none of his friends could learn from him the real reason for the final failure of the scheme.

Goldsmith had always a great interest in the Orient and in 1761 he drew up a memorial to Lord Bute in which he suggested a scientific mission to Aleppo, of which Goldsmith was to be the head, to inquire into the useful arts, inventions, and customs of the East with the idea of bringing back to Europe methods unknown there. The Government paid no attention to the memorial except to disapprove it. No one could have been more unsuited than Goldsmith to lead such an expedition as Dr. Johnson pointed out in one of his characteristic pronouncements. "Of all men" said he, "Goldsmith is the most unfit to go upon such an inquiry. Sir, he would bring home a grinding barrow, which you see in every street in London, and think that he had furnished a wonderful improvement."

After the failure of his India appointment, he sought to be examined for a surgeon's mate in the Army. Records of the College of Surgeons showed that he appeared for examination at Surgeon's Hall, December 21, 1758, and was found *not* qualified.

In spite of this, in 1765 after the

publication of "The Traveller" his social and financial prospects were much changed for the better, and Sir Joshua Reynolds, always Goldsmith's sincere well wisher urged him to resume the practice of medicine and pointed out the advantages he could obtain from being known as the member of such a profession. It must be remembered that in eighteenth century England the social position of the physician was high, the large number of men of family and talent from Harvey and Sydenham to Meade, Garth and Arbuthnot in the medical fraternity having done much to bring it to a high plane. Goldsmith therefore took his friends advice and began again as a medical practitioner under more favorable circumstances than surrounded him in his first attempt. He was now a man of note in the world of letters, had many powerful friends, and was no longer pressed for funds. In spite of these advantages his practice did not flourish as he himself quickly tired of the restraints and responsibilities imposed by his profession. Most of his patients were among those who forgot to pay him and his fees in consequence did not come up to his expectations. Finally an apothecary questioned the dosage of a drug prescribed by Dr Goldsmith, and in the dispute the patient, a Mrs Sidebotham, sided with the pharmacist to the disgust of the Doctor who left the patient and practice in a passion. To Beauclerc he said, "I am determined to leave off prescribing for my friends." "Do so, my dear Doctor", answered the wit, "whenever you undertake to kill, let it be only your enemies."

Goldsmith's last illness and death

were attended with circumstances that led to considerable controversy at the time. The poet had suffered in 1772 from an attack of dysuria which may have been due to an old Neisserian infection, though it may of course have been a non-specific condition. At this time he had been treated by Dr James, a respectable physician of the day who was the author of a three volume Medical Dictionary, but is best known, however, by a secret prescription sold everywhere as "James' Powder". The sale of this powder made him rich. It was then common for remedies to be kept secret by reputable medical men so that his conduct was not as unethical as it would be considered today. The powder was a compound of calcium phosphate and antimony oxide, and was diaphoretic, emetic, or purgative in its action depending on the dose used. It survives now in the National Formulary as the pulvis antimonialis, or James' powder, where the dose is given as 0.2 gram or 3 grains. Goldsmith had used this remedy under James' direction with relief of his symptoms and had apparently conceived an exaggerated idea of its value. In the early part of 1774 he had an exacerbation of his cystitis and his general health seems to have been impaired. He became quite ill on March 25, and sent for Mr Hawes whose account was published shortly after Goldsmith's death.

The following is the narrative of Mr Hawes.

"On Friday, the 25th of March, at 11 o'clock at night, the late Dr Goldsmith sent for me to his chambers. He complained of violent pain extending all over the forepart of his head, his tongue was moist, he had no cold

shiverings, or pain in any other part, and his pulse beat about 90 strokes in a minute. He then told me he had taken two ounces of ipecacuanha wine as a vomit, and it was his intention to take Dr James' Fever Powder. I replied that, in my opinion, this was a medicine very improper at that time, and begged he would not think of it. But I am sorry to say that every argument used seemed to render him more determined in his opinion; which gave me much concern, as I could not avoid thinking that the man whom I had every reason in the world to esteem was about to take a step which might prove extremely injurious to him. I therefore endeavoured to reason medically with him and observed that his complaint appeared to be more a nervous affection than a febrile disease. However, though I reasoned with him on the subject for near half an hour by his bed-side, and vehemently entreated him not to take Dr James' Powders, yet I could not prevail upon him to say he would not. At least I addressed him, to the best of my remembrances in the following manner:

" 'Please, Sir, to observe, that if you do take the fever powder, it is entirely without my approbation, and, at the same time, remember how very anxious I have been to persuade you to desist from doing it, and now I will take my leave, if you will be kind enough to grant me one request.' He very warmly asked me what that was. I told him that, as he had always consulted Dr Fordyce in preceding illness, and had expressed the greatest opinion of his abilities as a physician, I hoped he would permit me to send for him. It was full a quarter of an hour before I could obtain his consent to this, as the

taking of Dr. James' powders appeared to be the only object which employed his attention, and even then he endeavoured to throw an obstacle in the way, by saying that Dr Fordyce was gone to spend the evening in Gerrard Street, 'where', added he, 'I should also have been, if I had not been indisposed' "

Fordyce, an M D from Edinburgh in 1758 and a member of the Johnson circle, now took over the case but not until the poet had obtained from Hawes some James' powders which on taking he declared were not of proper composition and made him worse. He continued to grow worse, and became very drowsy and weak with a pulse ranging from 120 to 140 and an irregular low temperature.

On Sunday night, April 3, he fell into a deep sleep, at four o'clock in the morning of April 4, he was seized with a convulsion and expired an hour later.

His death was thus announced in the 'Public Advertiser' of April 5: "Yesterday morning died, much and deservedly regretted, at his chambers in Brick Court, in the Temple, Dr Oliver Goldsmith, author of the poems of the *Traveler*, and *Deserted Village*, and many ingenious works in prose. He was seized on Friday night with a nervous fever in his brain, which occasioned his death."

A considerable controversy arose as to what effect the popularly used James' Powder had on the course of his illness, some declaring that it had hastened his end, others defending it. A rumor arose that Dr Goldsmith believed that there had been a mistake in the compounding of the powder and this rumor became so troublesome that

Hawes published a brief account of the affair, apparently to defend himself against gossip

Just what the exact diagnosis was is not known but it is clear that an infection of the genito-urinary tract was the basic condition and the injudicious use by the patient, against the advice of his medical attendant, of a powerful irritating emetic and purgative produced a gastro-enteritis as well. Hawes and, indeed, all the medical men who attended Goldsmith, appeared to have done all that was possible.

Hawes became a man of mark, was a friend of Reynolds and of Goldsmith and the fact that he managed the latter's affairs and disposed of his effects after the poet's death indicates that Goldsmith's friends did not consider him remiss in any important particular. Hawes was made a Doctor of Medicine in 1780. He died at his birthplace, Islington, in 1808.

Goldsmith's death excited very little attention among the public as a whole but there was a general mourning among all his friends and associates to whom his simplicity and kindness of heart greatly endeared him. If one were to attempt to convey an idea of this good natured friendliness in a single incident it could perhaps be best done by quoting the concluding line of one of his letters to a member of a country family. After asking that his respects and regards be given to the members of the family he adds "And if there is an old dog in the family pat him on the head for me"

After Goldsmith's coffin had been closed it was opened again at the urgent request of the Jessamy Bride, the lovely Mary Horneck, that she might cut off a lock of his hair. This memento

of the poet she treasured through her long life (she did not die until 1840) and the memory of her affection and devotion have in the words of Irving, "hung a poetical wreath above her grave"

Sympathy and kindness were nearly the only attributes that Goldsmith possessed that fitted him for the practice of medicine. In all other respects few could have been so unfitted by nature for so exacting a profession. He was careless and impatient of restraint, with little idea of responsibility. His knowledge was of a miscellaneous and impractical kind and he never seems to have been a serious student.

As both a poet and a prose writer Goldsmith holds a high place in English literature. His smooth and flowing prose is unsurpassed by any English writer, except Addison, and his graceful verse was distinguished in a literary age celebrated for the quality of its poetry.

A little known fact regarding Goldsmith is the influence his writings had upon the life and work of Goethe. This influence is to be distinctly seen in Goethe's thought and life and was acknowledged by him in terms that deserve to be repeated. He expressed it strongly in his autobiography and in 1830 when he was eighty-one years of age, in a letter to Zelter he said "It is not to be described, the effect that Goldsmith's *Vicar of Wakefield* had upon me, just at the critical moment of mental development. That lofty and benevolent irony, that fair and indulgent view of all our infirmities and faults, that equanimity under all changes and chances, and the whole train of kindred virtues, whatever names they bear, proved my best edu-

cation, and in the end they are the thoughts and feelings which have reclaimed us from all the errors of life" Further he mentions that he has recently read "the charming book again from beginning to end" As Foster expresses it "The strength which can conquer circumstances; the happy wisdom of irony which elevates itself above every object, above fortune and misfortune, good and evil, death and life, and attains to the possession of a poetical world, first visited Goethe in the tone with which Goldsmith's tale is told"

Johnson, who at times had borne an

almost parental relation to Goldsmith, scolding him for his shortcomings in the parental style, loved him and felt his death the most keenly of any of the warm circle of friends with the possible exception of Sir Joshua Reynolds It was Johnson who composed the epitaph inscribed on a marble tablet beneath the medallion bust in the Poets' Corner of Westminster Abbey, beginning,

Olvarii Goldsmith,
Poetae, Physici, Historici

and ending,

Obiit Londini,
April IV, MDCCLXXIV

BIBLIOGRAPHY

Life of Oliver Goldsmith, John Foster
Life of Oliver Goldsmith, Washington Irving
Life of Oliver Goldsmith, Austin Dobson
Life of Oliver Goldsmith, Wm Black
(English Men of Letters)
"18th Century Vignettes", Austin Dobson
Macauley's Essay on Goldsmith

Boswell's Life of Johnson
Hawes and Newberry's statements regarding
last illness and death of Oliver Goldsmith
Edition of Goldsmith's poems illustrated by
Cope and others
Edition of Goldsmith's complete works

Editorial

THE NATURE AND ETIOLOGY OF HODGKIN'S DISEASE

Aside from the reported discovery of various organisms in the involved tissues in Hodgkin's disease, the implication that this condition is of infectious origin has been found in histological rather than clinical evidence. Neither geographical distribution nor age and sex incidence points in any significant way to a parasitic etiology. Of epidemiological aspects there are none save the not infrequent appearance of Hodgkin's disease in more than one member of a family, but this occasional observation is far less impressive than the familial incidence of certain other diseases, such as the retinal neuroblastoma, for instance, in regard to the neoplastic nature of which there is no difference of opinion. Also, when the invariably fatal outcome is considered in connection with the non-vital character of the structures first giving clinical evidence of involvement, no support for a belief in an infectious origin can be found. With those infectious diseases which entail the highest mortality, at least an occasional victim survives.

From the histopathological standpoint, however, Hodgkin's disease presents features which strongly suggest an infectious granuloma. Such are the variety of the microscopical changes and particularly the simultaneous occurrence of multiple cell types, lymphoblasts, fibroblasts, eosinophils, and var-

ious giant cells, all tending as the process advances to give way to a mature or hyaline fibrosis on the one hand, or to pass into caseation necrosis on the other. It was some years ago that the writer was warned by the distinguished director of a certain European pathological institute to be particularly careful in the postmortem examination of a case of Hodgkin's disease, because "young men are especially susceptible to the infection." The sincere solicitude of the advisor was appreciated, but without conviction as to the gravity of the danger. Yet it must be acknowledged that the complex histopathology of Hodgkin's disease does invite the assumption that this disease is a chronic infectious granuloma, a view which is still entertained by many competent pathologists.

The recent work of L'Esperance¹ has encouraged those committed to the parasitic etiology of Hodgkin's disease, especially since Ewing has given some measure of support to this view. L'Esperance believed that the tubercle bacilli which she obtained from a case of Pel-Ebstein disease were of the avian type. From these studies she deduced that the avian tubercle bacillus probably has an etiological relationship to Hodgkin's disease. Is this but another episode in sequence with the many assertions and suggestions which have

¹L'ESPERANCE, E. S. Study of case of Hodgkin's disease in a child, Jr Immunol., 1930, LVIII, 127-132

gone before? Tubercle bacilli of strains unspecified, diphtheroids, pleomorphic cocci, amebae, and monilia have each been given a rôle, playing an aggressive or a timid part depending upon the degree of caution possessed by their respective proponents. The very multiplicity of these claims raises doubt that there is a parasitic cause, while many who believe that Hodgkin's disease is infectious in nature are driven to the conclusion that the etiological agent has not yet been discovered.

Through an experimental and analytical investigation Medlar² has advanced well-considered and significant opinions in respect to the changes and responses of the hematopoietic and lymphoid tissues to infection with the avian tubercle bacillus, and in regard to the essential nature of Hodgkin's disease. He found that the histopathology induced by intravenous infection of normal and of vaccinated rabbits with virulent avian tubercle bacilli was not significantly different from that produced by other types of tubercle bacilli. The differences in gross and microscopic pathology caused by tubercle bacilli of the avian, bovine and human types are to be explained by differences in virulence, in susceptibility and in dosage, and are not specific for type of infecting organism. The important differences produced by the avian bacillus in vaccinated and non-vaccinated animals demonstrated this point. In

normal rabbits infection with avian bacilli produced constant lesions in the bone marrow. Among these were discrete collections of mononuclear leucocytes, sometimes necrotic, with varying degrees of infiltration with neutrophils. The hematopoietic tissue of the marrow was always hyperplastic, with numerous mitotic figures and increased megakaryocytes. Coincident with these changes in the marrow, there was an increase in the circulating mononuclear leucocytes. The megakaryocyte seemingly plays an important rôle in acute avian tuberculosis in the rabbit.

These observations of Medlar bring to mind those occasional examples in man in which a blood picture simulating an atypical leukemia is produced by an overwhelming miliary tuberculosis. One case known to the writer was believed to be an unusual leukemia on the basis of the increased number and preponderance of young mononuclear cells in the circulating blood. At autopsy rupture of caseous bronchial nodes into a pulmonary artery was demonstrated, and the bone marrow showed countless miliary foci of necrosis and young tubercles.

In Medlar's animals which had been infected intravenously with virulent avian tubercle bacilli, there were no gross pathological lesions simulating Hodgkin's disease. Microscopical examination showed in the lungs, liver and spleen a few to many giant cells which were indistinguishable from the giant cells seen in Hodgkin's lesions. The bone marrow in these animals was markedly hyperplastic and showed a marked increase of megakaryocytes. These were found in the process of entering the circulation as well as within

²MEDLAR, E. M. Avian tuberculosis in normal and vaccinated rabbits, *Am. Jr. Path.*, 1931, vii, 475-489. The significance of lesions resembling Hodgkin's disease in tuberculosis, *ibid.*, 491-497. An interpretation of the nature of Hodgkin's disease, *ibid.*, 499-513.

the blood sinuses of the marrow. These findings led to the conclusion that the giant cells observed in the tissues were also megakaryocytes. These lesions, suggestive of Hodgkin's disease, were not found in animals, which, by reason of smaller dosage or partial protection through vaccination, were able to survive for several months or longer. Moreover, essentially the same lesions were produced in experimental animals inoculated with virulent bovine and human tubercle bacilli, when the course of the disease was rapid but not when death occurred after a longer interval. Thus it appears that the avian organism has no monopoly on the production of this type of reaction. The megakaryocytes in the acutely tuberculous animals Medlar found to be closely similar to the Sternberg giant cells of Hodgkin's disease. But the presence of megakaryocytes in the circulation and lodged as emboli in the capillaries of the lungs is not a condition peculiar to acute tuberculosis. It is not specific for any condition, but occurs in various toxic and infectious states.

Medlar never observed the pleomorphism of cells or the other cellular appearances of true Hodgkin's disease in his experimental animals, and concluded that not only is Hodgkin's disease not produced by any type of tubercle bacillus but that no infectious agent can be the etiological factor. On the contrary his investigations led him to the belief that Hodgkin's disease is

a malignancy of the bone marrow for which the megakaryocyte is the type cell, and that the characteristic histopathology of Hodgkin's disease is explainable as a pleomorphic aggregation of cells which represent the developmental cycle of the megakaryocyte. The origin of lesions outside of the bone marrow he believed to be due to metastasis. The term "megakaryoblastoma" was suggested to designate true Hodgkin's disease.

The new element in Medlar's analysis is the designation of the megakaryocyte as the stem cell for the origin of Hodgkin's disease and the consequent localization of a primary focus in the bone marrow. It will not be easy to prove that the process by which the disease becomes generalized is one of metastasis and not simply the manifestation of a neoplastic system dyscrasia. May it not be true that cells potentially capable of giving rise to premegakaryocytes are to be found widely distributed in the reticulo-endothelial system outside of the bone marrow? The 'myeloid' reaction is seen in many situations in the body, such as the submucosa and subserosa of the bladder, for instance, where it appears to have arisen *de novo*. At any rate, these stimulating papers by Medlar give added support to the view that Hodgkin's disease is a neoplastic process genetically related to lymphoblastoma, myeloma, chloroma and the leukemias.

Abstracts

The Plantar Reflex, its Significance, the Methods of its Examination and the Causes of Some Diagnostic Errors By THEODOR DOSUZZOV, M D (The Jr of Nerv and Ment Dis, 1932, LVV, 374-383)

The plantar reflex should be examined with the patient in the dorsal position, with his extremities extended and with the feet resting on the heels. A blunt needle or a pin should be the instrument used and never an object with a wide end, such as the handle of the neurologic hammer. In making the examination the pin should be traced slowly along the internal and external edges of the foot-sole from the heel to the elevation above the metatarsophalangeal joint, but not on that elevation. The reactions that are to be observed are (1) movement of the toes, (2) tension of the 'm tensoris fasciae latae', (3) movement in the big joints (talocrural, knee and hip). The movement of the toes has been the most studied. Its normal display, plantar flexion and adduction, is present in from 88 per cent to 98 per cent of normal persons in various series studied. The modifications of this reflex can be both quantitative and qualitative. Of the qualitative modifications inversion is the most important, but of this 'Babinski's phenomenon' there exist several varieties. The complete form displays itself in the dorsal flexion of all five toes. A frequent form is that of dorsal flexion of the first toe and plantar flexion of the other four. This is the form frequently meant when the presence of Babinski's phenomenon is mentioned in case reports. Other forms are dorsal flexion of the first toe or of all toes, appearing upon irritation of the external side only of the sole of the foot, while irritation of the internal side produces the normal reflex, and inconstant inversion of the reflex, alternating with the normal form of plantar reflex or with its entire absence. All of these phenomena have the same significance. They

practically always mean a lesion of the pyramidal system. Diagnostic errors dependent upon the plantar reflex fall into two main groups. One of these is derived from technical faults of which the most common are an incorrect position for the patient during the examination, the use of an unsuitable instrument (usually the handle of a neurologic hammer), and the examination of the reflex from the part of the sole of the foot below the toes (by which method the positive Babinski's phenomenon may be caused to appear in healthy persons). The other group depends upon incorrect appreciation of properly obtained facts. Here the chief cause of error lies in ignoring the 'physiological Babinski', 'peripheral Babinski', 'pseudo-Babinski', 'pseudo-Puusepp', and 'pseudo-pathological Babinski'.

"Bothriocephalus Anemia" — Diphyllobothrium Latum and Pernicious Anemia By IVAR W. BIRKELAND, M D (Medicine, 1932, XI, 1-139)

The fish tapeworm has been reported in more than 250 cases of infestation of human beings on the continent of North America. At least twenty-three cases have been reported in patients who have spent their entire lives in this part of the world. The frequency of infestation is increasing so that the fish tape-worm is now estimated to be the most common cestode in the North-Central States and Central Canada. In New York City, as well as in Chicago and Minneapolis, the numerical predominance of this parasite over the pork and beef tapeworms has been recognized. While a majority of those harboring the fish tapeworm suffer no ill effects therefrom, some show a variety of clinical manifestations without anemia, with symptoms referable to the central nervous system or to the alimentary tract. In nonanemic carriers there may be noted an altered blood picture which has been defined as an abortive form of *Diphyllobothrium anemia*. When

present, the fully manifest anemia runs true to type with but very few exceptions, and as a rule it is indistinguishable from cryptogenetic pernicious anemia, clinically, hematologically, and pathologically. Achlorhydria is present in about 84 per cent of cases of *Diphyllobothrium* anemia. When hydrochloric acid is present, the acidity is usually below the average level. The incidence of spinal cord changes in association with this type of anemia has not been thoroughly investigated. Numbness and tingling in the hands and feet are not uncommon complaints. Prior to the recognition of the etiologic significance of the tapeworm in relation to this anemia, the same grave prognosis prevailed as for cryptogenetic pernicious anemia until the introduction of treatment with liver. Systematic anthelmintic measures have greatly reduced the mortality, and the cure of the anemia thus obtained is remarkably permanent. Since in Finland only one of 5,000 to 10,000 carriers of this worm develops a definite anemia, it is obvious that the worm cannot be the sole factor involved in the production of the anemia. Peculiarities of the constitution—racial, familial, and individual—must have to do with the ultimate susceptibility which makes the development of this type of anemia possible. This means a specific predisposition for the development of anemia of the pernicious type.

The National Leper Home (United States Marine Hospital), Carville, La. Review of the More Important Activities during the Fiscal Year Ended June 30, 1931. By O. E. DENNEY, F. A. C. P., Surgeon, United States Public Health Service. (Public Health Reports, 1932, xlvii, 601-613.)

During the fiscal year ending June 30, 1931, the average daily population of The National Leper Home at Carville, La., was 322. Sixty-three new patients were admitted, 3 absconded, of whom one returned within one month at his own expense, 9 patients who had absconded in previous years returned for hospitalization, 5 of them paying their own expenses. Nineteen patients were paroled. Of the 337 patients in the hospital on June 30, 1931, 178 were taking chaulmoogra oil

by mouth, the dosage varying from 5 to 125 drops three times a day. About one-third of the patients were taking chaulmoogra oil with benzocaine by intramuscular injection twice weekly, the average dose being 5 cc. Of the 49 patients who had been taking the intramuscular treatment for two years, 33 were markedly improved, 14 were moderately improved, and 2 were slightly improved. Of 131 patients who had taken treatment for over 12 months, 66 showed marked improvement, 50 showed moderate improvement, 8 showed slight improvement, and 7 were unchanged. Of the two groups, 34 were bacterioscopically negative. Forty-eight patients were treated with the ethyl esters of hydnocarpus. Intramuscular injections of the esters in doses of 2 or 3 cc. were given once a week and proved much less irritating than the esters of chaulmoogra oil. The beneficial results were about equal to those obtained with the ethyl esters of chaulmoogra oil. The sera of all new patients were examined by the Kolmer quantitative complement fixation method and Kahn precipitation test. Of the 110 examinations made by each method, 49 sera were negative by both Kolmer and Kahn methods, 24 were negative by Kolmer and positive by Kahn, 10 of which showed a 3 plus or higher reading by the Kahn method, and 6 were negative by Kahn and positive by Kolmer, all but 3 of which, however, showed a weakly positive reading by the Kolmer method.

The Present Status of BCG Vaccination. By S. A. PETROFF, Ph.D. (The New England Journal of Medicine, 1932, ccvi, 436-439.)

No problem in tuberculosis, since the famous controversy on the entity of bovine and human tuberculosis some twenty-five years ago, has created such a feverish discussion as the prophylactic immunization against tuberculosis known as BCG vaccination. From study of three different cultures of BCG, obtained at different times and from three different sources, the last directly from Professor Calmette, Petroff came to the conclusion that BCG was an organism of low virulence, producing tuberculous changes which had the tendency to heal. But with each of the three cultures, a small number of ani-

mals which had been under observation for about eighteen months developed progressive tuberculosis. The organism isolated from the lesions of these animals, when inoculated into healthy guinea pigs produced a progressive disease which could be transferred in a series of animals. Dissociation phenomena may be appealed to to explain the instability of the organisms and the resulting variation in virulence. The differentiation of human and bovine tubercle bacilli by animal inoculation is at present inadequate. Among the cultures obtained from human material, a large number cannot be classified as either human or bovine. As to the Lubeck disaster, Petroff does not believe that the vaccine used for the babies was contaminated with human type tubercle bacilli, but that reversion of the virulence had taken place. Petroff is strongly opposed to the use of a living virus as a vaccine against tuberculosis. An organism which is now nonvirulent may regain its virulence after passing through a suitable environment and in time may become a menace to the person who has been vaccinated.

Über Ulkuszunge [Ulcer Tongue] By PROF. DR. K. GLAESSNER (Arch. f. Verd.-Krankh., 1932, 11, 68-73)

In patients with gastric or duodenal ulcer there is frequently found a characteristic change in the tongue consisting of solitary or multiple epithelial defects. These occur chiefly in the posterior segment of the tongue, either in the mid-line or anterior to the circumvallate papillae. They are frequently symmetrical but may be unilateral and exhibit a defect which lays bare the corium. They are round or oval, frequently elongated, are entirely superficial, non-painful and give the impression of superficial ulcers. In size they range from 2 to 8 mm. in diameter. Glaessner has seen these lesions in more than 50 cases. Their presence speaks for peptic ulcer, but their absence must not be taken as evidence against an ulcer diagnosis. Once present, the tongue lesions appear to remain as long as the gastric ulcer persists. With its healing they disappear. The author believes this to be a hitherto undescribed form of glossitis characteristic for peptic ulcer.

Reviews

A Diabetic's Own Cook Book By STELLA H. LYONS, with a foreword by LOGAN CLENDENING, M.D., F.A.C.P., XII + 94 pages. Alfred A. Knopf, New York City, 1932. Price, \$2.00.

Mrs. Lyons is a good cook—and also a diabetic. How often, when faced with the common "hospital" list of foods useful for this ailment, has the physician been told "I'd rather die than diet!" Certainly, in her little volume "A Diabetic's Own Cook-Book", Mrs. Lyons has taken the "die" out of "diet". And—blessed relief to the diabetic,—she has done it without entangling him in a mass of weighing-scales, measuring glasses and logarithm-like tables of figures. In fact, the only evidence of these bug-a-boos lies on the title page set up by the publisher. After a common-sense layman's talk to the layman, dealing with the principles of feeding necessary to diabetics, Mrs. Lyons plunges at once into her main task, food and how to cook and

serve it. It's good food, too, food which any non-diabetic could and would enjoy. Moreover, the recipes, practically, are criticism-proof from the technical viewpoint. These recipes should prove most helpful not only to diabetics but also to dietitians in institutions who have "worn out" their stock meal-lists and to physicians who wish to put "life" into the sober lists of "allowed" foods as set forth in standard books on dietetics. Not in the least in value is the wholesome, "good housewife" optimism which pervades Mrs. Lyons' brochure. Steffanson startled the professional North Pole chaser with his book entitled "The Friendly Arctic", Mrs. Lyons similarly has removed a host of horrors by her courage in being "friendly" toward diabetes and its demands of "eating to live".

FRANK SMITHIES, M.D., M.A.C.P.

Italian Medicine By ARTURO CASTIGLIONI, M.D., Professor of the History of Medi-

cine, Royal University of Padua, Italy. Translated by E. B. Krummhaar, M.D., Professor of Pathology, University of Pennsylvania. vi + 134 pages. 11 illustrations. Paul B. Hoeber, Inc., New York City, 1932. Price, \$1.50.

Italian Medicine is the sixth member of the Clio Medica series. Like its predecessors it provides in readily portable form—in a coat pocket size, in fact—a readable survey of a limited field in medical history. It is intended to orient the reader in the special domain of the subject. The sponsors of the series are fortunate in securing an eminent Italian scholar of the History of Medicine as author. The translation is also excellent. It has a literary value of its own and is free from the idiom of the original. The reviewer questions the suitability of the subject for a Clio Medica volume. Would it not have been better to have subdivided the topic in order to permit fuller treatment? The author himself writes, "The history of Italian medicine is too vast and complex to be concentrated in a small volume. I have tried merely to outline its history in its high points from the time of the school of Salerno to the present day. It would not be possible even to name all the famous schools and illustrious physicians." The typography is good and the binding serviceable. In a modestly priced volume an excellent reference handbook to the more significant men and events in Italian Medicine is provided. If the subject proved too large for treatment in so small a compass, all the more does this book whet the appetite for a larger portion, and this is one of the aims of Clio Medica.

Female Sex Hormonology. A Review. By WILLIAM P. GRAVES, A.B., M.D., F.A.C.S., Professor of Gynecology at Harvard Medical School, Surgeon-in-Chief to the Free Hospital for Women and to the Parkway Hospital, Brookline, Massachusetts. 131 pages, 9 illustrations. W. B. Saunders Company, Philadelphia and London, 1931. Cloth, \$3.00.

This little book is in truth an interesting review of female sex hormonology. The author first deals with the very earliest work which proved the ovary to be a gland of internal secretion. He briefly reviews the

sex cycles in animals. After discussing the cycle in the ovary, he describes the uterine cycle and its correlation with that of the ovary. This relationship is clearly illustrated with diagrams. The author reminds the reader how closely the last phase of the endometrial change imitates an early decidual change, a fact of some importance. The animal experimental work is described which led to the isolation of the two ovarian hormones and the functions of these hormones, the finding of "folliculin" in various tissues of the female and even in the male and in plants. Later it was found that the corpus luteum also secretes a specific hormone, which prepares the uterus for the reception of the embryo. It has been proven that the secretion of the follicle and of the corpus luteum are antagonistic and are also synergistic. The author questions whether these two known hormones are simple or complex. The work leading to the development of the Ascheim-Zondek test, and the subsequent finding of at least two hormones of the anterior lobe of the hypophysis and their correlation with the ovarian hormones are fully presented. These investigations have led to new theories of menstruation, parturition and lactation. The author constantly emphasizes the rhythm of the sexual cycle in all its functions. The lack of success in organotherapy in the past he believes to be due largely to the use of extracts from the wrong organ. At the end of the book is a useful glossary and under the definition of "hormone" is a list of some of the proprietary hormone preparations, classified as to source. There is also an extensive bibliography. This book is stimulating and well worth reading.

Síndrome de Oclusión Coronaria [The Syndrome of Coronary Occlusion] By ANTONIO BARRIO, Médico Agregado del Hospital Nacional de Clínicas, Médico Inspector del Dispensario Público Nacional Antituberculoso de Belgrano, Adscripto a la Catedra de Clínica Médica. 214 pages, 111 figures. Librería "El Arteneo", Buenos Aires, 1930.

This is an excellent monograph on occlusive disease of the coronary arterial system. The first 38 pages are given over to anatom-

ical considerations and are supplied with excellent illustrations, in part from Spalteholz and other sources, and in part original. The next section deals with the physiology of the coronary circulation, including the coronary vasomotor mechanism and the action of certain drugs. A brief discussion of etiologic factors is followed by a description of the clinical syndrome of myocardial infarction. In the remaining sections the following topics are presented: An experimental and clinical study of coronary occlusion by the electrocardiograph, the evolution of the syndrome, the pathological anatomy of coronary occlusion, the clinical forms of the syndrome, differential diagnosis, prognosis, and treatment. The bibliography contains 188 titles, and there is a table of contents in outline form.

Clinical Atlas of Blood Diseases. By A. PINEY, M.D., M.R.C.P., Director of Pathological Department, The Cancer Hospital, London, Consulting Pathologist, Chelmsford Hospital, and STANLEY WYARD, M.D., M.R.C.P., Physician, The Cancer Hospital, London, and Princess Beatrice Hospital. Second edition. xvi + 105 pages. 38 illustrations of which 34 are in color. P. Blakiston's Son and Company, Inc., Philadelphia, 1932. Price, \$4.00 net.

This small book combines the functions of an hematological atlas and of a concise textbook upon the diseases of the blood. The necessity for a second edition within two years of the first is sufficient evidence that the work is supplying an actual need. The color plates, for the greater part, give the appearances of the various types of blood cells as stained by the Jenner-Giemsa method, at a magnification of 1,000 diameters. A brief, and therefore necessarily somewhat dogmatic, account of almost all hematological diseases is provided. The omission of any reference to ovalocytosis is noted, but sickle cell anemia has both a color plate and a discussion. A glossary of hematological terms, brief expositions of the Arneth and Schilling indices, 'family trees' of the various blood cells, and an all too brief appendix on the technic of blood examination are included. This book can be fully recommended for its purpose. The price is justified by the numerous figures in colors.

How's Your Blood Pressure? By CLARENCE L. ANDREWS, M.D., F.A.C.P., Attending Physician and Medical Chief at the Atlantic City Hospital. x + 225 pages. The Macmillan Company, New York City, 1931. Price, \$2.50.

This little book is written for "the victims of blood pressure psychology who live in constant fear of some impending calamity which may never occur." Couched in simple language intended to elucidate the subject of blood pressure for the laity, free use is made of homely similes to illustrate the physiology and anatomy of the circulation. The author takes up first in a general way the need for a circulatory system, then treats of some of the factors concerned with the maintenance of the blood pressure in health and disease. The general facts concerning blood pressure and its variations are accurately stated and no exception can properly be taken to the author's advice for the maintenance of a sound circulation. That faulty blood pressure is not a disease *per se*, is constantly kept before the reader. Perhaps, in an effort to state his thesis simply, the author has erred in the direction of excessive simplicity of style and in the presentation of facts already well known to intelligent laymen, but sound advice, sympathetically set forth, characterizes this thoroughly wholesome book.

Das Chlorophyll als Pharmakon [*The Pharmacology of Chlorophyll*]. By PROF. DR. EMIL BURGI. 84 pages, 28 graphs. 1932, George Thieme, Leipzig. Price, M. 6.40.

In this well-printed monograph various pharmacologic aspects of chlorophyll are considered in detail. Such are its part in the synthesis of hemoglobin and development of erythrocytes, its further effects upon the blood picture, its tonic effects upon the organism as a whole and upon certain organs and tissues, and its dosage and therapeutic availability. Two and one-half pages of bibliographic references to chlorophyll are appended.

ADDITIONAL BOOKS RECEIVED

Proceedings of the Twenty-Fifth Annual Convention of The Association of Life Insurance Presidents (GEORGE T. WICHT,

- Secretary, 165 Broadway, New York City) 278 pages 1931
- Annual Report of the Surgeon General of the Public Health Service of the United States for the Fiscal Year, 1931* vii + 354 pages United States Government Printing Office, Washington, D C 1931 Price 85 cents, bound in cloth
- Origin of Cancer The Specific Cancer Cell of Carcinoma, Contrasted with the Normal Matrix Embryonal Cellule of Primul Ovum Days, to 8th Week, [etc]* By FRANK A STAHL, M D, Chicago, Ill 96 pages, 1932 Privately printed
- Prohibiting Minds and the Present Social and Economic Crisis* By STEWART PATON, M D, Lecturer on Psychiatry, Johns Hopkins University, Baltimore vii + 198 pages Paul B Hoeber, Inc, New York City, 1932 Price, \$2.00 (See quotation on p 1403)
- Experimental Studies of Dengue* By JAMES STEVENS SIMMONS, Major, Medical Corps, United States Army, JOE H ST JOHN, Major, Medical Corps, United States Army, and FRANCOIS H K REYNOLDS, Captain, Veterinary Corps, United States Army viii + 489 pages, 3 plates and 159 text figures Monograph 29 of the Bureau of Science, The Government of the Philippine Islands Bureau of Printing, Manila, 1931
- Semiologia de la Onda T del Electrocardiograma y su Interpretacion Clinica* [Semiology of the T Wave of the Electrocardiogram and its Clinical Interpretation] By ANTONIO BATTRO 121 pages, 66 illustrations Sebastian de Amorrotu, Ayacucho, 774, Buenos Aires, Argentina
- The Cause of Cancer* By W E GYE, M D, and W J PURDY, M B, Members of the Scientific Staff of the National Institute for Medical Research, London. xiv + 515 pages, 105 illustrations Cassell and Company, Ltd, London, Toronto, Melbourne, Sydney, 1931 Price, 30 shillings net

College News Notes

Acknowledgement is made of the receipt of gifts to the College Library of publications by members, as follows

- Dr Edward E Cornwall (Fellow), Brooklyn, N Y—1 reprint,
- Dr Hyman I Goldstein (Associate), Camden, N J—1 reprint,
- Dr Robert A Knox (Fellow), Washington, Pa—1 reprint,
- Dr William Gerry Morgan (Fellow), Washington, D C—1 reprint,
- Dr Frank Garm Norbury (Fellow), Jacksonville, Ill—1 reprint,
- Dr Lea A Riely (Fellow), Oklahoma City, Okla—1 reprint,
- Dr Karl Rothschild (Associate), New Brunswick, N Y—1 reprint

Dr Lea A Riely (Fellow), Oklahoma City, Okla, addressed the Fourteenth Quarterly Session of the Southern Oklahoma Medical Association, March 8, 1932, on "Diseases of the Gall Bladder"

The following Fellows of the College presented papers at an afternoon symposium sponsored by the Henry Ford Hospital, Detroit, Mich, on January 29, 1932

- Dr Frank R Menagh, Detroit,—“Food Hypersensitiveness and Hypothyroidism as Etiological Factors in the Treatment of Chronic Eczema”
- Dr John G Mateer, Detroit,—“Dietary, Foreign Protein, and Nervous Factors in the Treatment of Chronic Irritable Colon”
- Dr Frank J Sladen, Detroit,—“Chronic Undulant Fever—A Food-borne Disease Problem”, and later, in conjunction with another physician, Dr Sladen held a “Clinical-Pathological Conference”

Dr Erwin D Funk (Fellow), Wyomissing, Pa, has been in Berlin, Germany, the last three months studying the relation of hospitals to communities, and hospital management under a grant from the Oberlaender

Trust and Carl Schurz Foundation Later he will go to Vienna

Dr Elliott P Joslin (Fellow), Boston, Mass., was awarded the Kober Medal by the Association of American Physicians, at a meeting of the Association in Atlantic City on May 4. The medal was awarded to Dr Joslin because "for many years, he has been one of the world's leading authorities on diabetes mellitus. He has carried on important researches in this field. He has simplified and standardized treatment. He has been a great educator in the management of diabetes. He has trained doctor, nurse and patient in the use of his methods both individually and by group instruction. His textbook on diabetes, which has gone through four editions is a mainstay of both physician and medical student. His small manual is the bible of the diabetic patient. It is believed that his life work represents a type of sustained and scholarly performance for which Dr Kober would have been glad to see his prize awarded."

Dr Leonard G Rowntree (Fellow), Rochester, Minn., has been appointed Director of the Philadelphia Institute for Medical Research, which will open its doors next fall at the Philadelphia General Hospital, according to a statement issued recently by Dr Judson Daland (Fellow), Philadelphia, President of the Institute and one of its founders in 1922. Opening of the Institute will give Philadelphia, according to Dr Daland and his colleagues, a research organization with few rivals the world over. In addition to its own research work, the new Institute will hold itself ready to cooperate in medical research by collaboration or affiliation with any or all medical and allied institutions desirous of establishing such relationship. It will occupy a somewhat analogous position to that held by the Thorndike Institute of Boston. Dr Rowntree, the new Director, was graduated in medicine at the University of Western Ontario in 1905. Since that time he has held many posts of importance among which are the following: associate professor of medicine at Johns Hopkins University School of Medicine, chief of the department of medicine of the University of

Minnesota, member of the Air Service Medical Staff in France during the World War, senior medical consultant and director of Clinical Investigation of the Mayo Clinic.

The following Fellows of the College appear on the Medical Advisory Board of the Institute: Dr S Solis-Cohen, Dr Joseph C Doane, Dr D J McCarthy, and Dr Jefferson A Clark.

Dr E J G Beardsley (Fellow), Philadelphia, addressed the Woman's Auxiliary of the Burlington County Medical Society at the Community House, Moorestown, N J., on Monday, March 21. His subject was "Never Changing Truths Concerning Medicine and Life."

Dr Ralph deBallard Clarke (Fellow), Meriden, Conn., took part in a symposium on collapse therapy at the Danbury (Conn.) Hospital on February 9, 1932. At this time he addressed members of the Danbury Medical Society and physicians from surrounding towns on the subject "Phrenicectomy and Artificial Pneumothorax in Tuberculosis of Children", illustrating his talk with X-ray films of cases under compression-therapy among children at Undercliff, the Connecticut State Childhood Tuberculosis Sanatorium at Meriden, Conn.

Dr Roland N Klemmer (Fellow), Lancaster, Pa., was elected Medical Director of the Lancaster County Hospital, Lancaster Pa., at a recent meeting of the newly organized Staff.

Dr Albert E Russell (Fellow), Washington, D C., was detailed by the Public Health Service to give an address on "Silicosis and Tuberculosis" at a joint meeting of the Trudeau Club and the St Louis, Mo., Medical Society on April 5, 1932.

Dr Lewis J Moorman (Fellow), Oklahoma City, is President of the Southern Medical Association.

Dr Charles Hartwell Cocke (Fellow) Asheville, N C., Governor for North Carolina, is Second Vice-President of the same body.

An Experimental Basis for Intravenous Vaccine Therapy in Chronic Arthritis With a Summary of Results Obtained in Patients*†

By B J CLAWSON, M D , and M WETHERBY, M D , *Minneapolis, Minn*

THE factors considered as a basis for intravenous streptococcic vaccination reported in this paper are (1) etiology and (2) a method of vaccination which will not produce hypersensitiveness (allergy) and will desensitize patients already hypersensitive and will produce a high degree of protective immunity

ETIOLOGY

The belief that most cases of chronic arthritis are infectious in origin is quite generally accepted. The exact infectious agent and the manner and form in which the agent finds its way into the joints are not so generally agreed upon. Some people believe that there is a direct infection of the joint by the living organisms. Others look upon the lesions in the joint as a response to inanimate parts of the infectious agent which lives in some remote focus. The etiology of chronic arthritis has been studied from the bacteriological, immunological, and pathological standpoints

Bacteriology Streptococci have been recovered from chronic arthritis in higher percentages and by a greater number of workers than any other organism. The materials cultured have been the blood, the joint fluid and tissues, the lymphnodes, and the subcutaneous nodules. The number of cases and the sources of the materials cultured with the percentage of positive streptococcic cultures obtained by many workers are given in tables 1, 2, 3, 4, and 5. The average percentage of positive streptococcic cultures obtained are as follows: blood, 35 per cent, joint fluids, 35 per cent, joint tissues, 44 per cent, lymphnodes, 61 per cent, and subcutaneous nodules, 72 per cent. Twelve hundred and ninety-seven cultures have been reported. Five hundred and twenty (40 per cent) were positive for streptococci (table 6). Recent workers have raised these percentages very decidedly.

The kind of streptococci recovered has, in the main, been *Streptococcus viridans*. Beta hemolytic streptococci have been found in a small percentage of the cases. Cecil, Nicholls and Stansby⁴ most frequently recovered atypical hemolytic streptococci.

The strains studied by us have in most cases cross agglutinated with one

Presented at the San Francisco meeting of the American College of Physicians, April 6, 1932.

From the Departments of Pathology and Medicine of the University of Minnesota.

TABLE 1
Bacteriology of Chronic Arthritis Blood

YEAR	AUTHOR	NO OF CASES	NO POS	PER CENT POS	KINDS
1917	Moon and Edwards ¹	123	32	26	S viridans
1920	Richards ²	104	15	14	S viridans
1927	Hadjopoulos and Burbank ³	145	15	10	S viridans
1929-1931	Cecil, Nicholls and Stainsby ⁴	154	96	62	S viridans and atypical S hemolyticus
1931	Klugh ⁵	74	53	72	S viridans
1931	Dawson, Olmstead and Boots ⁶	80	2	2.5	S viridans
1931	Gray and Gowan ⁷	71	41	58	S viridans
1931	Wetherby and Clawson ⁸	50	25	50	S viridans 24 S hemolyticus 1
	Total	801	279	35	

TABLE 2
Bacteriology of Chronic Arthritis Joint Fluid

YEAR	AUTHOR	NO OF CASES	NO POS	PER CENT POS	KINDS
1920	Richards ²	54	4	7	S viridans
1922	Billings, Coleman and Hibbs ⁹	14	6	43	S viridans
1928	Forkner, Shands and Poston ¹⁰	60	11	18	S viridans
1930	Shands ¹¹	33	17	52	S viridans 14 S anhemolyticus 2 S hemolyticus 1
1931	Cecil, Nicholls and Stainsby ¹²	49	33	67	S viridans and atypical S hemolyticus
1931	Gray and Gowan ⁷	8	5	62.5	S viridans
	Total	218	76	35	

TABLE 3
Bacteriology of Chronic Arthritis Joint Tissues

YEAR	AUTHORS	TISSUES CULTURED	NO OF CASES	NO POS	PER CENT POS	KINDS
1902	Poynton and Paine ¹³	Synovial membrane	1	1	100	Diplococcus
1928	Cecil, Nicholls and Stainsby ¹²	Head of femur	2	2	100	Atypical S hemolyticus
1930	Margolis and Dorsey ¹⁴	Epiphyseal marrow and bone	15	7	47	S viridans 1 S anhemolyticus 3 Diphtheroids 3
1930	Margolis and Dorsey ¹⁴	Synovial membrane	14	4	29	S viridans 2 Diphtheroids 2
	Total		32	14	44	

TABLE 4
Bacteriology of Chronic Arthritis Lymph Glands

YEAR	AUTHOR	NO OF CASES	NO POS	PER CENT POS	KINDS
1914	Rosenow ¹⁵	54	32	59	S viridans
1922	Billings, Coleman and Hibbs ⁹	27	21	78	S viridans 19 S hemolyticus 1 Mixed 1
1928	Forkner, Shands and Poston ¹⁰	20	9	45	S viridans
1928	Baer ¹⁶	10	7	70	S viridans and S hemolyticus
1929	Poston ¹⁷	117	69	59	S viridans 67 S anhemolyticus 2
	Total	228	138	61	

TABLE 5
Bacteriology of Chronic Arthritis Subcutaneous Nodules

YEAR	AUTHOR	NO OF CASES	NO POS	PER CENT POS	PERCENT POS	KINDS
	Billings, Coleman and Hibbs	1	1	100		S viridans
1932	Clawson and Wetherby	17	12	71		S viridans
	Total	18	13	72		

another and equally well with strains of acute rheumatic origin. The strains of streptococci from both acute rheumatic fever and chronic arthritis have in our experience tended to fall into a fairly well defined group which generally grew poorly when first isolated and produced a faint green discoloration on the blood agar plate when incubated at 37°C for 24 hours. These organisms do not seem to represent a specific strain.

Immunological Reactions The two immunological reactions studied in patients with chronic arthritis were (1) hypersensitiveness (allergy) as indicated by the skin test and (2) streptococcic agglutination.

Birkhaug¹⁸ showed by skin tests that patients having chronic arthritis

were hypersensitive to streptococcic protein in a higher percentage than normal persons. We obtained similar results in a study of 127 cases of chronic arthritis and 107 normal persons (table 7).

Nicholls and Stainsby¹⁹ found that the serums of patients with chronic arthritis agglutinated streptococci in higher dilutions than the serums from normal persons. We tested the serums from 81 normal individuals and from 60 patients with chronic arthritis (table 8). The strain of streptococcus used had been isolated from a case of chronic arthritis. The greatest percentage of the serums of the normal people showed agglutination in the dilution of 1:400 and the greatest number of the chronic arthritics in the dilu-

TABLE 6
Bacteriology of Chronic Arthritis Summary

SOURCE	NO CASES	NO POS	PER CENT POS
Blood	801	279	35
Joint fluid	218	76	35
Joint tissues	32	14	44
Lymphnodes	228	138	61
Subcutaneous nodules	18	13	72
	1297	520	40

TABLE 7
Intradermal skin tests with *Streptococcus viridans* in patients with chronic arthritis

CONDITION	NO CASES	NO POSITIVE	PER CENT POSITIVE
Chronic arthritis	127	112	88.1
Normal persons	107	53	49.5

TABLE 8
Streptococcic Agglutination in Normal People and in Patients with Chronic Arthritis

DILUTIONS	1:0	1:50	1:100	1:200	1:400	1:800	1:1600	1:3200	1:6400	1:12800
NORMAL, 81 CASES		1	5	2	18.5	44	26	2	0	0
CHRONIC ARTHRITIS, 60 CASES		0	0	1.6	6.6	31.6	38.3	10	10	1.6

tion of 1 800 Only 28 per cent of the normal persons showed agglutination above 1 400 The per cent above 1 400 in the chronic arthritic patients was 60

The higher percentage of positive skin tests and streptococcic agglutination titers in patients with chronic arthritis suggests a possible etiological relationship of the streptococci to chronic arthritis

Pathological Findings The cellular reactions in the joint capsules and membranes as described by Nichols and Richardson,²⁰ Margolis and Dorsey,¹⁴ and others were polyblastic in character and decidedly resembled those described by Swift²¹ in joint lesions in acute rheumatic fever

We observed subcutaneous nodules in 30 per cent of a series of 300 cases of chronic arthritis We found the cellular reaction in these nodules, as did Coates and Coombs,²² to be similar to the reactions in subcutaneous nodules and heart valves in acute rheumatic fever and in heart valves in subacute bacterial endocarditis The reaction was also similar to that in subcutaneous nodules produced experimentally in rabbits by injecting streptococci

The bacteriological, immunological, and pathological findings described above tend to support a causal relation between streptococci and chronic arthritis

METHOD OF VACCINATION

An effort was made to see what could be done by vaccination toward protecting patients having chronic arthritis Animal experiments were carried on toward developing an efficient method of vaccination which

would give the highest degree of immunity against streptococci

The things necessary in a vaccine for chronic arthritis are (1) not to make the patient hypersensitive to the protein in the vaccine, (2) to desensitize the patients who are already hypersensitive, and (3) to bring about a high degree of protective immunity

The following experiments in rabbits showed that the intravenous injections of streptococci met the three above requirements while the subcutaneous injections did not

Hypersensitiveness (Allergy) The degree of tissue response as an indicator of hypersensitiveness is shown in table 9 The tissue response in terms of percentage was compared in normal, hypersensitive, and immune rabbits The hypersensitiveness was produced by injecting animals subcutaneously in one area with a mixture of agar and streptococci The immune state was brought about by repeated intravenous injections of streptococci Each of the animals in the three groups was then injected subcutaneously in each of ten places on the back with a known number of streptococci All animals were killed five days later and the number and the size of the nodules at the sites of the small multiple subcutaneous injections were determined The tissue response (cellular reaction) in these nodules was similar to the type of reaction found in lesions in chronic arthritis The tissue response in the normal animals was 3 2 per cent, in the hypersensitive animals, 88 per cent, and in the immune animals, 1 1 per cent The average streptococcic agglutination titer in the hypersensitive animals was 1 3200, and in the immune animals,

1 200,000 These experiments confirmed the findings of Swift²³ in that animals injected subcutaneously were made hypersensitive while the animals injected intravenously were not The subcutaneous method of giving a vaccine will not desensitize the hypersensitive animals, for hypersensitiveness is produced and maintained by subcutaneous injections

Desensitization Ten animals were made hypersensitive as described above and later vaccinated intravenously with *Streptococcus viridans* The degree of tissue response, indicative of hypersensitiveness in these ten vaccinated animals, was compared with that in hypersensitive animals which had not been vaccinated (table 10) The non-vaccinated hypersensitive animals showed 88 per cent of tissue response The hypersensitive animals which had been vaccinated intravenously gave a tissue response of 52 per cent The average agglutination titer in the non-vaccinated hypersensitive animals was 1 3200, and in the vaccinated hypersensitive animals, 1 50,000 The hypersensi-

tive animals were desensitized by the intravenous method of vaccination The intravenous method met the two necessary requirements in not bringing about a state of hypersensitiveness (table 9) and in desensitizing animals which were already hypersensitive (table 10). As far as hypersensitiveness is concerned the intravenous method of vaccination rather than the subcutaneous method should be used

Protective Immunity It was seen in the preceding experiments that the streptococcic agglutination titers were decidedly higher in animals injected intravenously than in animals injected subcutaneously To test the protective merits of the subcutaneous and intravenous methods of injecting a streptococcic vaccine two groups of animals were selected Group 1 was vaccinated subcutaneously at five weekly intervals with one billion killed streptococci Group 2 was vaccinated intravenously at the same periods with the same doses The streptococcic agglutination titers of the two groups were then determined (table 11) The animals vac-

TABLE 9

Percentage of Tissue Response to Subcutaneous Injections of Streptococci in Normal, Hypersensitive (Allergic), and Immune Animals

NO	NORMAL	HYPERSENSITIVE	IMMUNE
1	03 per cent	10 per cent	01 per cent
2	01	6	02
3	02	9	00
4	01	8	00
5	02	10	02
6	03	8	02
7	20	10	00
8	00	10	02
9	00	8	00
10	00	9	
	32 per cent	88 per cent	11 per cent

Average Agglutination titers

NORMAL	1 25
HYPERSENSITIVE	1 3200
IMMUNE	1 200,000

TABLE 10
Change in Percentage of Tissue Response to Subcutaneous Injections of Streptococci in Hypersensitive Animals Following Intravenous Vaccination (*S. viridans*)

NO	NOT VACCINATED	VACCINATED
1	10 per cent	00 per cent
2	6	00
3	9	00
4	8	00
5	10	00
6	8	00
7	10	00
8	10	0.2
9	8	5.0
10	9	0.0
	88 per cent	5.2 per cent
Average Agglutination Titers		
NOT VACCINATED		1 3200
VACCINATED		1 50,000

TABLE 11
Relative Immunity Produced by Subcutaneous and Intravenous Vaccine Treatment

NO	NORMAL	SUBCUTANEOUS	INTRAVENOUS
1	1 50	1 3200	1 400,000
2	1 100	1 6400	1 200,000
3	1 0	1 3200	1 400,000
4	1 0	1 1600	1 400,000
5	1 0	1 1600	1 400,000
	1 30	1 3200	1 360,000

cinated subcutaneously had titers ranging from 1 1600 to 1 6400. The animals vaccinated intravenously had titers of from 1 200,000 to 1 400,000. If the height of the agglutination titer can be relied upon as an indicator of the degree of immunity, then it is obvious that a much higher degree of protection can be produced against streptococci by intravenous injections than by subcutaneous injections of a vaccine.

The evidence of a correlation between the height of an agglutination titer and protection was shown by comparing the rate at which streptococci were killed in normal animals and in animals which had a high agglutination titer and by comparing the bactericidal power of the blood of vaccinated and

non-vaccinated chronic arthritic patients.

Normal rabbits and rabbits highly immune to streptococci were injected intravenously with 50 million live streptococci. In 15 minutes 1 c.c. of blood was taken from the heart of each animal and plated on agar. In two hours the animals were killed and a gram of liver from each animal was ground in a mortar and plated in dilutions on agar. It was found in the series of ten rabbits of each group that the rate of disappearance of the streptococci from the blood in 15 minutes was three times greater in the immune than in the normal animals (table 12). The rate at which the streptococci were killed in the livers of the animals in

two hours was 33 times greater in the immune animals (table 13). The streptococcic agglutination titers averaged 145 in the normal animals and 170,000 in the immune animals.

It was found by using the method of Sutliff and Rhoades²⁴ for determining the bactericidal power of whole blood that the whole blood of vaccinated chronic arthritic patients with an agglutination titer of 16400 or more had a much greater bactericidal power for

streptococcic agglutination than the blood of non-vaccinated patients with an average streptococcic agglutination titer of 1200 (table 14).

Since the agglutination titer rises decidedly higher by the intravenous method of vaccination than by the subcutaneous method and since the above experiments in animals and patients showed a correlation between an elevated agglutination titer and desensitization and protective immunity, the

TABLE 12

Organisms per Cubic Centimeter Alive 15 Minutes after Injecting 50,000,000 Streptococci Intravenously into Normal Animals and Animals Made Immune to Streptococci

NORMAL		IMMUNE	
AGGLUTINATION TITER	NO PER C C	AGGLUTINATION TITER	NO PER C C
150	55	1200,000	5
150	40	1200,000	30
1100	41	1200,000	10
1100	44	150,000	13
150	40	1200,000	8
1100	47	1200,000	13
10	50	150,000	17
10	70	1200,000	21
10	23	1200,000	14
10	25	1200,000	16
145	435 ₂	170,000	147 ₁

TABLE 13

Number of Streptococci Alive in a Gram of Liver Two Hours after Injecting 50,000,000 Organisms into Normal and Immune Animals

NO	NORMAL		IMMUNE	
	AGGLUTINATION	NO PER GRAM	AGGLUTINATION	NO PER GRAM
1	10	3,500	1400,000	650
2	150	4,200	1400,000	2,500
3	10	7,000	1400,000	600
4	10	2,500	1100,000	300
5	10	4,500	1100,000	1,500
6	150	2,250	1200,000	1,350
7	150	10,200	1400,000	4,000
8	1100	10,000	1200,000	2,800
9	10	5,600	1400,000	1,000
10	10	6,000	1200,000	2,000
	125	55,750	1280,000	16,650
		33+		1

intravenous method of administering a vaccine would seem to be the one of choice

Type or Species Specificity in Desensitization and Protective Immunity If desensitization and immunity should be type (strain) specific, then it would seem that autogenous vaccines should probably be used in most cases. If, on the other hand, these two phenomena should be only species (group) specific, then a stock streptococcic vaccine would in most cases likely be sufficient. This is an important consideration, for it would be impracticable to use autogenous vaccine in treating chronic arth-

ritis in most cases. Experiments were carried on with animals to determine the relation of acquired desensitization and immunity to type and species specificity.

Animals made hypersensitive to *Streptococcus viridans* of acute rheumatic origin were vaccinated intravenously with *Streptococcus hemolyticus* from a case of puerperal sepsis. The degree of tissue response to *Streptococcus viridans* indicative of hypersensitivity was determined and compared with non-vaccinated animals which had been made hypersensitive to *Streptococcus viridans* (table 15). The

TABLE 14
Comparison of the Bactericidal Power and the Agglutination Titers (1:6400 or more) of the Blood of Treated and Untreated Patients with Chronic Arthritis

GROUP	NO. OF STREPTOCOCCI KILLED PER C.C.		AGGLUTINATION TITERS	
	VACCINATED	NOT VACCINATED	VACCINATED	NOT VACCINATED
1	40,000	0	1:6400	1:100
2	52,000	0	1:6400	1:200
3	38,000	3,800	1:6400	1:400
4	25,000	0	1:12800	1:400
5	163,000	0	1:6400	1:100
6	160,000	1,600	1:12800	1:800
7	32,000	320	1:25000	1:3200
8	36,000	360	1:6400	1:200
9	3,200	50	1:6400	1:200
10	3,800	0	1:12800	1:100
	90	1		

TABLE 15
Change in Percentage of Tissue Response to Subcutaneous Injections of Streptococci (*S. viridans*) into Hypersensitive Animals (*S. viridans*) following Intravenous Vaccination (*S. hemolyticus*)

NO.	NOT VACCINATED	VACCINATED
1	10 per cent	00 per cent
2	6	00
3	9	00
4	8	00
5	10	00
6	8	00
7	10	00
8	10	00
9	8	02
10	9	02
	88 per cent	04 per cent

response in the non-vaccinated animals was 88 per cent and in the animals vaccinated with *Streptococcus hemolyticus*, 0.4 per cent. The desensitization did not seem to be type specific.

In a series of ten animals each animal was immunized with a different strain of streptococcus of chronic arthritic origin and later each of the animals was injected with 50 million organisms of another strain of streptococcus. The rapidity with which this organism disappeared from the blood (tested in 15 minutes) and from the liver (tested in two hours) was much greater than in normal animals. These experiments suggested that protective immunity also was not type specific.

Non-specific Protein Therapy (B typhosus) in Streptococcal Infections
Intravenous injections of *B. typhosus* are commonly used in treating chronic arthritis. Experiments were performed in animals to see what relation intravenous injections of *B. typhosus* bore to the desensitization of animals hypersensitive to *Streptococcus viridans*

and to the protection of animals against *Streptococcus viridans*.

Animals were made hypersensitive to *Streptococcus viridans* and vaccinated intravenously with *B. typhosus* (table 16). The tissue response to *Streptococcus viridans* in these animals was compared with the response in non-vaccinated hypersensitive animals. The response in the non-vaccinated animals was 88 per cent and in the animals vaccinated with *B. typhosus*, 82 per cent, as compared with 0.7 per cent in the hypersensitive animals vaccinated with streptococci. It was concluded that desensitization to streptococci was not brought about by a non-specific protein reaction.

Animals vaccinated intravenously with *B. typhosus* developed a high agglutination titer to *B. typhosus* but the titer to *Streptococcus viridans* was raised but slightly. When these animals were injected intravenously with 50 million streptococci it was found that the rate at which the streptococci disappeared from the blood was even less

TABLE 16

Change in Percentage of Tissue Response to Subcutaneous Injections of Streptococci in Hypersensitive Animals following Intravenous Vaccination (*B. typhosus*)

NO	NOT VACCINATED	VACCINATED
1	10 per cent	10 per cent
2	6	8
3	9	10
4	8	5
5	10	8
6	8	5
7	10	10
8	10	10
9	8	6
10	9	10
	88 per cent	82 per cent
Average Agglutination Titers		
NOT VACCINATED		1 3200
VACCINATED		1 4000
Streptococcus		1 6400
B typhosus		

than in normal animals (table 17) Protection against streptococci was not brought about by intravenous vaccination with *B typhosus*

It can be concluded on fairly good experimental grounds that streptococcic desensitization and protection are species specific but not type specific and that they are not brought about by a non-specific protein reaction

The above findings and experiments supply the following conclusions as a basis for intravenous streptococcic vaccination in chronic arthritis

1 Non-specific chronic arthritis in most cases appears to be due to a

streptococcic infection (not a specific strain)

2 Subcutaneous injections of a streptococcic vaccine do not desensitize the hypersensitive individual but tend to increase the hypersensitive state

3 The subcutaneous method develops only a slight degree of protection

4 The intravenous method of giving a streptococcic vaccine desensitizes the hypersensitive patient, does not develop hypersensitivity, and does cause a high degree of protective immunity to be developed

TABLE 17

Organisms per Cubic Centimeter Alive in the Blood 15 Minutes After Injecting 50,000,000 Streptococci Intravenously into Normal Animals and Animals Made Immune to *B Typhosus*

NORMAL		IMMUNE TO B TYPHOSIS	
AGGLUTINATION TITER	NO PER C C	AGGLUTINATION TITER	NO PER C C
1 50	55	Ty 1 100,000 St 1 200	75
1 50	40	Ty 1 100,000 St 1 200	55
1 50	40	Ty 1 100,000 St 1 200	75
1 800	41	Ty 1 200,000 St 1 200	60
1 0	18	Ty 1 400,000 St 1 0	32
1 50	30	Ty 1 100,000 St 1 200	87
1 100	40	Ty 1 50,000 St 1 400	40
1 0	21	Ty 1 100,000 St 1 200	41
1 200	21	Ty 1 100,000 St 1 100	15
1 100	40	Ty 1 50,000 St 1 200	50
	346 1		530 15

5 Neither the desensitizing nor the protective phenomena are type specific but they appear to be species specific. They are not of the nature of a non-specific protein reaction.

These conclusions were the basis of the experiments in the intravenous vaccine therapy in 301 cases of chronic arthritis reported in this paper.

SUMMARY OF RESULTS

Three hundred and one cases of chronic arthritis have received five or more intravenous injections at weekly intervals. The organism used in the vaccine was from a case of acute rheumatic fever and had been cultured for nine years, was of low virulence, did not agglutinate spontaneously, and was safe for intravenous injections. Cross agglutination occurred in high dilutions (1:50,000) with many other strains of both acute rheumatic and chronic arthritic origins.

Dose The initial dose was 100 million organisms. This was increased by 100 million organisms at weekly injections. As a rule not more than eight to ten injections were given.

Reactions Slight reactions with temperature and chills occurred in

about 50 per cent of the cases. The degree of reaction seemed to have no relation to the clinical improvement.

Number of Injections Necessary for Clinical Improvement Nearly two-thirds of the patients experiencing improvement did so after five injections, nine-tenths did so after seven injections. There were very few cases in which improvement took place, if it had not occurred with eight to ten injections (table 18).

Agglutination Titers and Vaccine Therapy The greatest percentage of untreated patients showed an agglutination titer of 1:200 with the strain of streptococcus used in the vaccine. The intravenous vaccine therapy stimulated a definite rise in the agglutination titers in the serums of most of the patients. Clinical improvement occurred most frequently when the titer was 1:6400 or more (table 19). The height of the streptococcic agglutination titer seemed to be a reliable indicator in most instances of the protection possessed by the patient against streptococci.

Results Determination of clinical improvement was based on three criteria: (1) decrease in pain, (2) decrease in joint swelling, and (3) increase in joint movement.

TABLE 18
Time of Beginning Definite Improvement

NUMBER OF TREATMENTS	1	2	3	4	5	6	7	8	9	10	Over 10
NUMBER IMPROVED	13	39	46	47	34	18	13	8	11	2	2
PERCENTAGE IMPROVED	5.6	16.7	19.7	20.2	14.5	7.7	5.7	3.4	4.7	1.3	1.3
TOTAL PERCENTAGE IMPROVED	5.6	22.3	42.0	62.2	76.7	84.5	90.2	93.6	97.4	98.7	100

TABLE 19
Distribution of Maximum Agglutination Titer in 188 Improved Treated Arthritic Patients

TITER	1:800	1:1600	1:3200	1:6400	1:12800	1:25000	1:50000	1:100000
NUMBER	4	9	27	54	71	20	3	0
PERCENTAGE	2.1	4.7	14.3	28.8	37.8	10.6	1.7	

TABLE 20
Results of Therapy (301 cases)

	NUMBER OF CASES	PER CENT
Definite clinical improvement	233	74.4
Questionable improvement	19	6.3
No improvement	49	16.3

Excluding the 19 questionable cases the results for the different criteria for improvement are tabulated as follows:

Definite clinical improvement was observed in 80 per cent of the cases treated.

DISCUSSION

An experimental basis for intravenous streptococcic vaccination in chronic arthritis and the results of such vaccination in 301 patients are discussed in this paper.

Streptococcic vaccination seems to be indicated because chronic arthritis appears to be due to a streptococcic infection. The things to be considered as evidence for the etiology of chronic arthritis are: (1) Streptococci have been recovered from the blood, joints, lymphnodes, and subcutaneous nodules from a relatively high percentage of cases of chronic arthritis. (2) A high percentage of patients having chronic arthritis are found by the skin test to

be hypersensitive (allergic) to streptococci. (3) The streptococcic agglutination titer is higher in patients with chronic arthritis than in normal persons. (4) The cellular reactions in lesions in chronic arthritis are similar to those of known origin, such as acute rheumatic fever and subacute bacterial endocarditis.

The intravenous method of administering the vaccine is indicated rather than the subcutaneous method for the following reasons: (1) The intravenous method does not produce hypersensitiveness, as does the subcutaneous method, but desensitizes the patient who is already hypersensitive to streptococcic protein. (2) Subcutaneous injections of streptococci produce only a slight degree of protection, while the intravenous method results in a high resistance.

An autogenous vaccine does not seem to be necessary since both the desensitizing and protective phenomena seem

TABLE 21

	NUMBER OF CASES	PER CENT
1. Joint pain (282 cases)		
Decreased pain	233	82.6
Unchanged	49	17.4
2. Joint swelling (197 cases)		
Decreased swelling	160	81.2
Unchanged	37	18.8
3. Joint motion		
Increased motion	206	84.7
Unchanged	37	15.3

to be species (group) specific rather than type (strain) specific

The use of intravenous injections of *B typhosus* in treating chronic arthritis is contraindicated, since such injections do not desensitize patients hypersensitive to streptococci and do not cause the development of a protective immunity in the patient against streptococci

Intravenous injections of streptococci can safely be administered to patients. Such injections in our series of 301 patients have resulted in definite clinical improvement in about 80 per cent of the cases

The streptococcic agglutination titer of the serums of these patients appears to be a reliable indicator in most cases of the protection possessed by the patient against streptococci.

These experiments have not been in effect long enough to draw definite conclusions concerning the duration of the clinical improvement. In a few cases the clinical improvement and a high agglutination titer have been sustained for as long as eight months

CONCLUSIONS

1 Intravenous streptococcic vaccination seems to meet the demand of a method of vaccination for chronic arthritis in not increasing hypersensitiveness, in desensitizing the already hypersensitive individual, and in producing a high protective immunity against streptococci.

2 The subcutaneous method seems to be contraindicated, since it tends to increase hypersensitiveness, does not bring about a state of desensitization, and produces only a low degree of protection

3 The intravenous injection of *B typhosus* in treating chronic arthritis would seem to be contraindicated

4 About 80 per cent of the patients with chronic arthritis who received five or more intravenous injections of a streptococcic vaccine showed definite clinical improvement

5 The results obtained in treating patients with chronic arthritis by intravenous streptococcic vaccination seem to justify the further study of such treatment.

REFERENCES

- ¹MOON, V C and EDWARDS, S H Results of blood cultures in rheumatoid arthritis, Jr Infect Dis, 1917, xxi, 154
- ²RICHARDS, J H Bacteriologic studies in chronic arthritis and chorea, Jr Bact, 1920, v, 511
- ³HADJOPOULOS, L G, and BURBANK, R A preliminary study bearing on the causative factors of multiple infectious arthritis, Jr Bone and Joint Surg, 1927, ix, 278
- ⁴CECIL, R L, NICHOLLS, E E and STAINSBY, W J The bacteriology of the blood and joints in chronic infectious arthritis, Arch Int Med, 1929, xliii, 571
- ⁵KLUGH, G F Streptococci from blood cultures in arthritis, So Med Jr, 1931, xxiv, 706
- ⁶DAWSON, M H, OLMSTEAD, M, and BOOTS, R H Bacteriological investigation on blood, synovial fluid and subcutaneous nodules in rheumatoid arthritis, Proc Soc Exper Biol and Med, 1931, xxviii, 419
- ⁷GRAY, J W, and GOWEN, C H The rôle of streptococci in arthritis deformans, Am Jr Med Sci, 1931, clxxxii, 682
- ⁸WETHERBY, MACNIDER, and CLAWSON, B J A study of chronic arthritis with special reference to intravenous vaccine therapy, Arch Int Med, 1932, xlix, 303-320

- ⁹BILLINGS, F , COLFMAN, G H, and HIBBS, W G Chronic infectious arthritis, Jr Am Med Assoc, 1922, lxxviii, 1097
- ¹⁰FORKNER, C E , SHANDS, A R, and POSTON, M A Synovial fluids in chronic arthritis, Arch Int Med, 1928, xlii, 675
- ¹¹SHANDS, A R Personal communication cited by FORKNER, C E The synovial fluid in health and disease with special reference to arthritis, Jr Lab and Clin Med, 1930, xv, 1199
- ¹²CFCIL, R L , NICHOLLS, E E, and STAINSBY, W J Bacteriology of blood and joints in chronic infectious arthritis, Proc Soc Exper Biol and Med, 1928, xxiv, 6
- ¹³POYNTON, F J, and PAINE, A The etiology of rheumatic fever, Lancet, 1900, ii, 861-869
- ¹⁴MARGOLIS, H M, and DORSEY, G H E Chronic arthritis bacteriology of affected tissues, Arch Int Med, 1930, xli, 121
- ¹⁵ROSENOW, E C The newer bacteriology of various infections as determined by special methods, Jr Am. Med Assoc, 1914, lxiii, 903
- ¹⁶BAER, W S Discussion of paper by Gibson, Jr Bone and Joint Surg, 1928, x, 753
- ¹⁷POSTON, M A Gland cultures in infectious arthritis, Jr Am Med Assoc, 1929, xciii, 692
- ¹⁸BIRKHAUG, K E Skin hypersensitiveness of patients with rheumatic fever and chronic arthritides to filtrates, autolysates, and bacterial suspensions of streptococci, Jr Infect Dis, 1929, xli, 363
- ¹⁹NICHOLLS, E E, and STAINSBY, W J Streptococcic agglutinins in chronic infectious arthritis, Jr Clin Invest, 1931, x, 323
- ²⁰NICHOLS, E H, and RICHARDSON, F L Arthritis deformans, Jr Med Res, 1909, xxi, 149
- ²¹SWIFT, H F Pathogenesis of rheumatism, Jr Exper Med, 1924, xxxix, 497
- ²²COATTS, V, and COOMBS, C F Observations on the rheumatic nodule, Arch Dis Child, 1926, i, 183
- ²³DERICK, C L , HITCHCOCK, C H, and SWIFT, H F Reactions of rabbits to non-hemolytic streptococci study of modes of sensitization, Jr Exper Med, 1931, lii, 1
- ²⁴SUTLIFF, W D, and RHOADES, D R The pneumococidal power of whole blood, Jr Clin Invest, 1930, ix, 55

Hypertension and Diabetes*†

By HENRY J. JOHN, M.D., F.A.C.P., *Cleveland, Ohio*

THAT the blood pressure rises as a result of increase in weight in non-diabetic individuals has been shown by various authors^{3, 11, 15, 16, 17, 18, 11}. One striking example of this relationship is shown in the data reported by Hartman and Ghrist¹⁰ of the Mayo Clinic, who in 1922 analyzed a series of 2,042 consecutive cases of this type which were seen there. The males and females were practically equally divided. The summary of this study may be expressed by the following

Blood pressure in the total number of cases of underweight (male)	125 1
Blood pressure in the total number of cases of overweight (male)	141 2
	(12 38 per cent)
Blood pressure in the total number of cases of underweight (female)	127 2
Blood pressure in the total number of cases of overweight (female)	142 2
	(11 81 per cent)

Observations by Terry¹⁷ and Rose¹⁸ showed that in patients presenting hypertension with obesity, merely the reduction of their weight brought about also a decrease in their blood pressure. Therefore, obesity may be looked upon as one of the etiological factors in the production of hypertension in non-diabetics.

If overweight is an important factor in hypertension how does the group of patients afflicted with diabetes stand

in relation to overweight? Such information should give us one of the clues to a further analysis of this question. In 1930, I¹⁰ published a study of a series of 528 cases of diabetes studied from the standpoint of weight at the time I saw them for the first time or at any time of their life. The following data were obtained from this study.

Normal weight (below normal and up to plus 10 per cent above normal) in 24 per cent
Overweight (above 10 per cent) in 76 per cent

It is evident then, that overweight is a definite factor in diabetes.¹⁰ The distribution of overweight in the various decades compared with normal weight is shown in chart I.

The weight factor is of course only one of the links in the chain of hypertension, but it is a significant one. The immediate causes of hypertension are still sufficiently uncertain to warrant a new hypothesis, for many causative factors have been suggested. For a brief review we may consider the following possible causes of hypertension: (1) arteriosclerosis in diabetes,^{24, 26, 27} (2) increase in cholesterol

*Received for publication, September 10, 1931

†From The Cleveland Clinic, Cleveland, Ohio

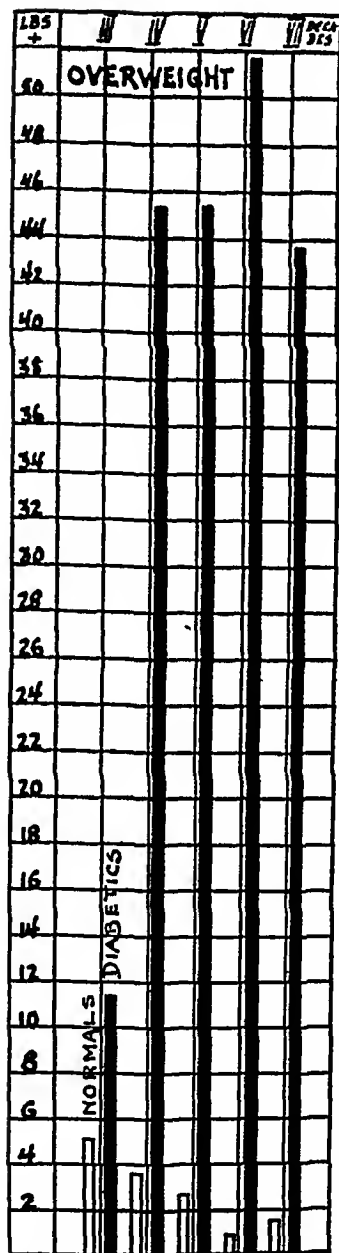


CHART I The distribution of overweight pounds in the author's series of 528 cases diabetes arranged according to decades

circulating blood,^{24, 25, 29, 30, 34, 35} (3) blood peptides,³⁸ (4) anemia brain,^{30, 38, 39, 40} (5) hyperglycemia,^{31, 32, 34, 35, 37} (6) insulin administration,³³ (7) hyperthyroidism, (8) ney disease,³⁶ (9) heredity,^{42, 63} (10)

syphilis,⁴³ (11) infections,^{44, 63} (12) high protein in diet,^{45, 46, 47, 68} (13) pressor effect of guanidine bases,^{48, 49} 50, 51, 52, 53, 54, 55, 56, 57, 58, 59 (14) lowered calcium content,^{61, 62} (15) toxemia of pregnancy,⁶³ (16) mental and physical strain,⁶³ (17) disturbance of the acid-base balance⁶⁸ Adams⁵ states that in 90 per cent of the cases of diabetes discussed in his paper (1,001 cases) the patients were more than 10 per cent overweight at some time before the onset of diabetes, 54 per cent were still overweight after having had diabetes for varying lengths of time. In this same series Adams points out that 162 per cent of the male diabetics had a systolic blood pressure of more than 150 mm as against 24 per cent of Exton's normal males, 267 per cent of the female diabetics had a systolic pressure of more than 150 mm as against 43 per cent of Exton's normal females. This is offset by the fact that in Adams' cases 156 per cent of male diabetics had a blood pressure lower than 110 mm as against 25 per cent of Exton's normal men, and 19 per cent of diabetic women had a systolic pressure of less than 110 mm as against 81 per cent of Exton's normal women. The apparent contradiction, Adams says, may be explained by the wide "scatter" of the blood pressure readings in diabetic patients as compared with the narrow scatter of blood pressure readings of normal persons.

The summary of Adams' study is shown in charts II and III. Chart II shows the blood pressure in all cases of diabetes as compared with that in a series of normals. Chart III shows the blood pressure in cases in which only diabetic patients who are free from

nephritis, arteriosclerosis and hyperthyroidism, are shown together with the normal series. He concludes that there is no appreciable increase of blood pressure in the diabetics over that of non-diabetics.

The range of opinion as to whether blood pressure is increased in the presence of diabetes can be noted from table I, in which I have tried to summarize the opinions of various authors on the subject. The consensus of opinion would seem to indicate that the blood pressure is increased in the presence of diabetes

My own studies comprise observations on 1,828 cases of diabetes mellitus. Of this group 1,385 cases are of diabetes mellitus and 443 are cases of diabetes mellitus associated with hyperthyroidism. Observations on blood pressures in diabetes, arranged according to decades, according to distribution between male and female are summarized in table 2. Throughout this study I have divided these observations arbitrarily into two groups. (1) cases in which the blood pressure has not exceeded 140 mm and (2) those in which the blood pressure is above 140

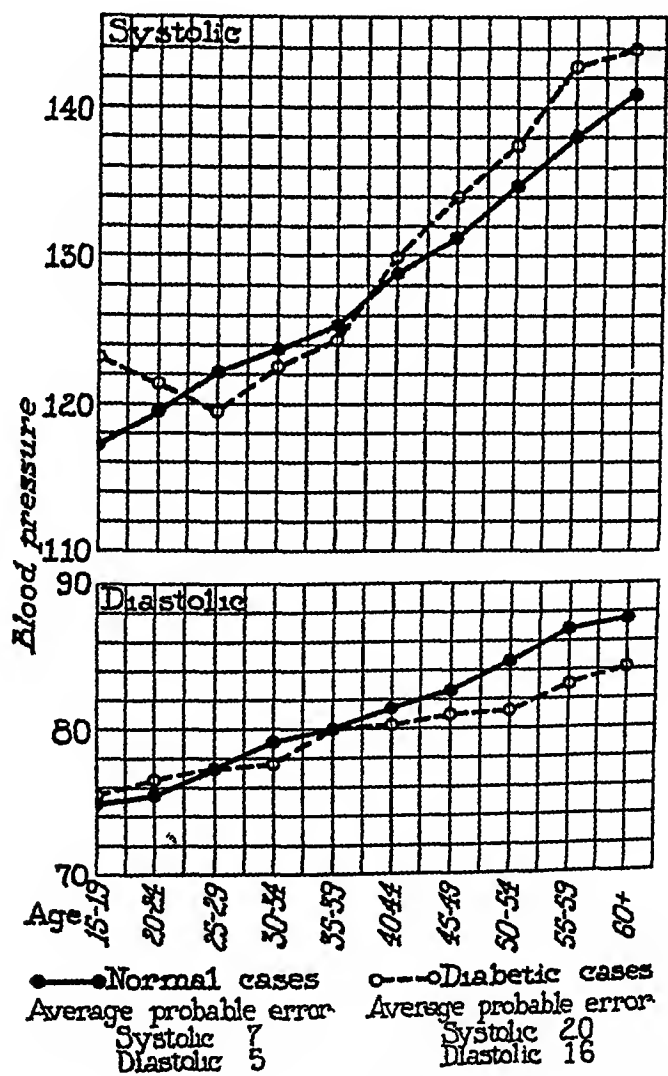


CHART II A comparison of the blood pressure of diabetic patients with the normal blood pressure (Adams⁵)

mm Details in regard to each group are given in each descriptive chart or table. It will be noted that the males and females were equally divided. Of the entire group, 54.3 per cent presented a blood pressure under 140 mm and 45.7 per cent had a blood pressure above 140. When we compare these data with the observations on non-diabetics furnished by Wiechmann⁴ as I have done in table 3, it will be seen in decades below and including the fourth the blood pressure is virtually the same in non-diabetics as it is in diabetics, while above this age the incidence of high blood pressure is greater in diabetics.

In order to further analyze the incidence of hypertension in non-diabetics I grouped a series of 11,840 cases from data furnished by Weitz, Gellman, Soller, Keith et al, Riseman and Weiss, Frost, Dublin, Fisk-Kopf, and Rogers-Hunter. The results of this analysis are presented in chart IV. It will be noted that the considerable increase in the incidence of hypertension begins with the fourth decade, and is greatest in the sixth decade after which it again declines.

Chart V shows a series of observations on my own cases in which the variation of blood pressure in various diseases is noted. A summary of the

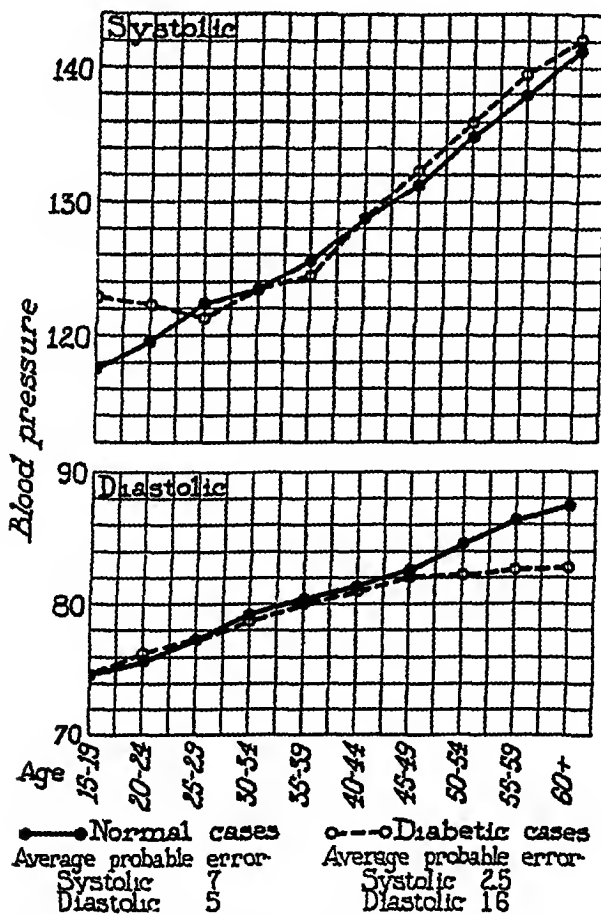


CHART III The blood pressure of diabetic patients free from nephritis, arteriosclerosis or hyperthyroidism, compared with normal blood pressures (Adams⁵)

TABLE 1A
Observations by Various Authors in Regard to Blood Pressure in Diabetes Mellitus

AUTHOR	YEAR PUBL	INCREASED	BLOOD PRESSURE	
			NORMAL	DECREASED
Adams ⁵	1929		*	
Koopman ⁶	1924	*		
Hitzenberger ⁷	1921	**	*	
Kylin ⁸	1921	**	*	
Katz-Klein ⁹	1924	*	*	
Peterson ¹⁰	1929	**	*	
Kramer ¹¹	1928	*		
Rosenbloom ¹²	1922	*	*	*
Elliott ¹³	1907		*	*
Larsen ²⁰	1929	*		
Kahn ³⁴	1921			*
Maranon ²¹	1922	*	*	
Riesman ¹⁰²	1919	*		
Hitzenberger ²²	1921	*		
Kylin ²³	1922	*		
Herrick ³⁵	1923	*	*	
Janeway ⁸²	1915	*	*	
Wiechmann ³⁷	1928	*		
von Noorden and Isaac ⁷⁸	1927	*		
Elliott ⁸³	1907		*	
Maranon ⁷⁹	1922	*		
Wiechmann ⁹⁶	1928	*		
Hitzenberger ⁸⁰	1921	*		
Joslin ⁸¹	1928	*		
Peiser ⁷⁵	1930	*		
John (present publ)	1931	*		

TABLE 1B
Observations of Various Authors in Regard to Blood Pressure in Non-Diabetics

AUTHOR	YEAR OF PUBL	BLOOD PRESSURE		
		INCREASED	NORMAL	
Faber ¹⁴	1927	*		(1000 normal children increased weight)
Symonds ¹⁵	1923	*		(150,419 normals with increased weight)
Huber ¹⁶	1927	**	*	(12000 army officers, normals)
Terry ¹⁷	1923	**	*	(Obese, non-diabetic, 58 per cent hypertension)
Rose ¹⁸	1922	**	*	(Normals, B P reduced by reducing weight)
Hartman and Ghrist ²	1929	*		(Normals with increased weight)

TABLE 2
Blood Pressure in Diabetes (John)

DECADE		TO 120	121 130	131 140	141 150	151 160	161 170	171 180	181 190	191 200	201 250	251	TOTAL	MALE	FEMALE
I	M	2											2	2	
	F	1											1		1
II	M	11	1										12	12	
	F	10	1										11		11
III	M	25	6	3	1	2							37	37	
	F	31	9	3	1	4	1		1				50		50
IV	M	55	20	9	4	2		1		1	1		93	93	
	F	29	25	15	10	5	2	2	1	1	6	2	98		98
V	M	67	23	19	14	6	5	3	2	2	4	1	146	146	
	F	25	19	22	30	15	15	13	8	5	9	2	163		163
VI	M	48	42	23	22	18	14	9	5	4	5	2	192	192	
	F	28	17	28	36	21	21	31	19	11	20	1	233		233
VII	M	23	19	22	22	16	15	9	11	6	13	1	157	157	
	F	11	14	11	15	12	11	10	7	5	11		107		107
VIII	M	12	8	6	10	7	4	2	3		1		53	53	
	F	4	2	3	2	2	6	1	4	1	3	2	30		30
Total		382	206	164	167	110	94	81	61	36	73	11	1385	692	693
Per cent		752—54.3%			633—45.7%									50%	50%

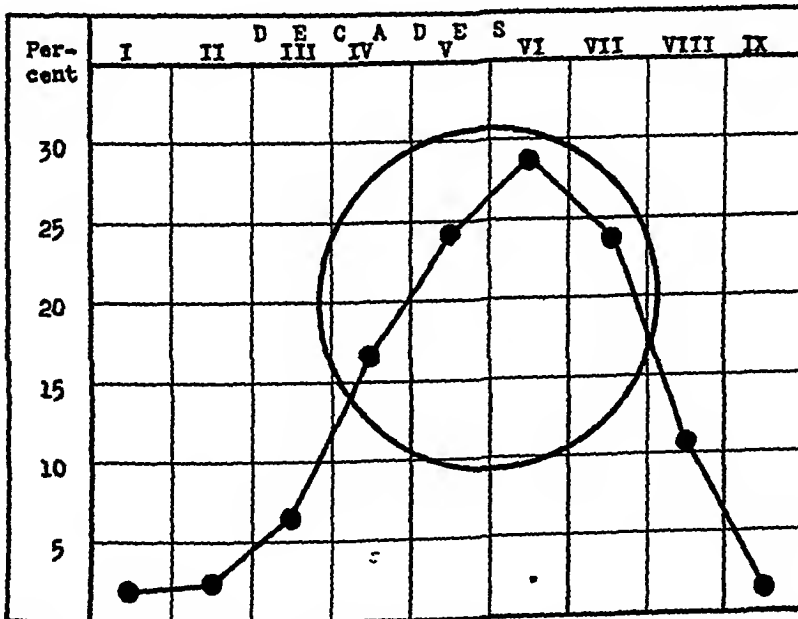


CHART IV The average incidence of hypertension in non-diabetics classified as to the different decades. A compilation from the literature of 11,840 cases by Westz, Gelmann, Zoller, Keith et al, Riseman and Weiss, Frost, Dublin-Fisk-Kopf, Rogers-Hunter

TABLE 3
Blood Pressure in Diabetes, in Diabetes-Hyperthyroidism and in Normals

AGE	BELOW 30 YEARS				31-40 YEARS				41-50 YEARS				51-60 YEARS				61-70 YEARS				71-80 YEARS			
BLOOD PRESSURE	NORMAL—PERCENT	DIABETIC—PERCENT (W)	DIABETIC—PERCENT (J)	HYPERTHYROIDISM AND DIABETES—PERCENT (J)	NORMAL—PERCENT	DIABETES—PERCENT (W)	DIABETES—PERCENT (J)	HYPERTHYROIDISM AND DIABETES—PERCENT (J)	NORMAL—PERCENT	DIABETES—PERCENT (W)	DIABETES—PERCENT (J)	HYPERTHYROIDISM AND DIABETES—PERCENT (J)	NORMAL—PERCENT	DIABETES—PERCENT (W)	DIABETES—PERCENT (J)	HYPERTHYROIDISM AND DIABETES—PERCENT (J)	NORMAL—PERCENT	DIABETES—PERCENT (W)	DIABETES—PERCENT (J)	HYPERTHYROIDISM AND DIABETES—PERCENT (J)	NORMAL—PERCENT	DIABETES—PERCENT (W)	DIABETES—PERCENT (J)	HYPERTHYROIDISM AND DIABETES—PERCENT (J)
MALES	197	27	51	8	107	13	93	19	126	36	146	33	96	48	192	31	57	23	157	8	12	7	53	3
70-109	15	26	74	26	17	38	60	11	13	8	46	25	10	2	25	16	5		15	12			23	
110-140	80	67	19	37	76	56	32	47	70	56	29	36	60	44	34	36	54	38	26	24	27	12	26	
141-160	5	7	7	25	6	6	6	37	16	20	14	27	20	20	20	38	24	33	24	24	41	43	32	
161-200				12	1		1	5		10	8	9	10	26	17	10	17	22	26	38	19	33	17	100
Above 200							1		1	6	3	3		8	4			7	9	12	13	12	2	
FEMALES	171	13	62	35	50	5	98	53	51	18	163	108	60	33	233	102	39	22	107	38	14	11	30	5
70-109	20	23	68	26	22		30	25	4	10	15	5	8	9	12	3	2	5	10	2			13	
110-140	76	77	20	40	75	80	40	28	70	40	25	27	55	28	19	20	26	14	23	4	29	36	17	20
141-160	4		9	35	3		16	26	19	10	28	30	30	18	25	27	37	25	26	26	29	18	13	
161-200			3	9		20	6	15	7	40	25	34	7	36	35	35	20	42	31	59	13	28	40	40
Above 200							8	6			7	4		9	9	15	15	14	10	9	29	18	17	40

(J)—John (present series)
(W)—E. Wiechmann (Munch med Wchnschr, 1929, lxxvi, 98-101)

TABLE 4
Blood Pressure in Hyperthyroidism and Diabetes (John)

DECADE		to 120	121 130	131 140	141 150	151 160	161 170	171 180	181 190	191 200	201 250	251	TOTAL	MALE	FEMALE
I	M F														
II	M F	1	1	3	1	1							7		7
III	M F	2 8	1 3	2 4	2 6		1 1		2				8 28	8	28
IV	M F	2 13	4 8	5 7	4 9	3 5		1 2	5		3		19 53	19	53
V	M F	8 6	9 15	3 15	3 18	6 14	1 16	2 5	9	6	1 4		33 108	33	108
VI	M F	5 4	7 8	4 12	8 16	4 11	1 8	2 12	9	6	14	2	31 102	31	102
VII	M F	1 1		2		2 5	1 5	1 10	5	1 2	3		8 38	8	38
VIII	M F			1			1	2 1	1		2		3 5	3	5
Total		51	58	58	72	55	36	37	32	15	27	2	443	102	341
Per cent		167-37 6%			276-62 4%									23%	77%

results of observations of cases of diabetes associated with hyperthyroidism (as shown in table 4), is given below in comparison with the results of observations on cases of diabetes. It will be noted that there is a definite increase in the incidence of hypertension in the latter, and also that three-fourths of these patients are females.

A study of these two relationships analyzed from a somewhat different angle, namely, that of dividing each of these groups into cases up to 30 years of age and above this age, as shown in table 5, shows that in the group of

young diabetics hypertension is present in only nine per cent as contrasted with an incidence of hypertension in 42 per cent of cases of diabetes with hyperthyroidism. In diabetes, then, increase in blood pressure begins later in life, whereas if diabetes is complicated with hyperthyroidism such a rise occurs early in more than 50 per cent of cases.

Kramer,¹¹ who analyzed 500 cases of diabetes and compared these with non-diabetics, found that 38 per cent have hypertension, that is, a blood pressure above 150 mm.

	MALE PER CENT	FEMALE PER CENT	BLOOD PRESSURE BELOW 140 MM PER CENT	BLOOD PRESSURE ABOVE 140 MM PER CENT
Diabetes	50	50	54.3	45.7
Diabetes and hyperthyroidism	23	77	37.6	62.4

THE RELATION OF HYPERGLYCEMIA TO HYPERTENSION

In 1910 Neubauer⁷⁶ noted the occurrence of hypertension associated with hyperglycemia and offered the theory that the excessive activity of the suprarenals might be the underlying factor. The question naturally arises—why should there be an excessive activity of the adrenals in old age? Even granting that the activity of the islands is lessened, due to arteriosclerosis or at any rate to a diminished blood supply, or to any other cause which might alter a normal activity of the adrenals thus bringing about hyperglycemia—yet the idea of an increase in the activity of the adrenal glands in old age does not seem logical. O'Hare⁷⁰ also noted the fact that there is a decline in tolerance for carbohydrates in *certain* examples of high blood pressure. He wrote "certain examples"—which indicates a general observation. Were the increase in blood pressure, *per se*, the only factor then we should find a decrease in tolerance for carbohydrates in all cases of progressively increasing blood pressure. He offered the explanation that sclerosis of the arteries of the pancreas might be the pathologic background for this condition. He

thinks that these cases are potential diabetic cases and need observation. On the other hand, Pearce and Keith⁷⁷ suggested that because a diseased kidney is unable to utilize the ordinary amount of sugar brought to it by the blood, a diminished sugar consumption results, together with increased accumulation of this substance in the blood stream. When one considers the total weight of the kidneys in relation to the weight of the rest of the body, it hardly seems possible that this would be the answer. Furthermore, when I think of the hun-

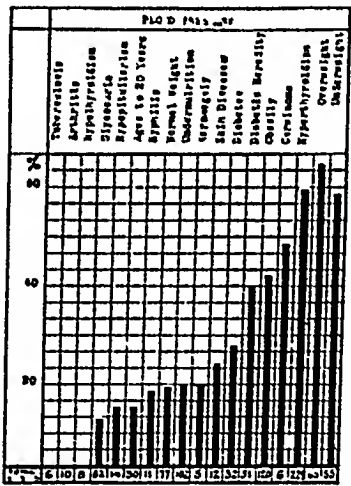


CHART V Chart showing the percentages of the cases in which the blood pressure was above 140 mm among the various groups classified according to affection (John)

TABLE 5

Study of Hypertension in Diabetes and Diabetes with Hyperthyroidism, the Cases Being Divided into Two Age Groups Those up to 30 and Those above 30 years of Age (John)

		DIABETES		DIABETES AND HYPERTHYROIDISM	
AGE (years)	BLOOD PRESSURE	NO CASES	PER CENT	NO CASES	PER CENT
1-30	Below 140	103	91	25	58
	Above 140	10	9	18	42
31-90	Below 140	647	51	141	35
	Above 140	621	49	258	65

dreds of renal conditions ranging from the mildest to the most severe, with but little kidney substance left functioning these patients meanwhile presenting repeatedly a normal blood sugar level, I feel quite strongly that diseased kidneys alone will not cause an appreciable rise in blood sugar. Meyers and Killian⁷³ noted an increase in the diastatic activity of the blood in examples of nephritis and expressed the idea that this might account for the hyperglycemia often noted in such cases. Harle,³⁶ in a study of a series of cases of hypertension, failed to discover any exact parallelism in the curves of blood pressure and blood sugar. He concluded that hypertension and hyperglycemia are not the common results of increased activity of the chromaffin system. Botti¹⁰³ stated that in the presence of hypertension the blood sugar is increased and the sugar tolerance lessened. Kylin⁸ has also described the association of lowered carbohydrate tolerance with hypertension. Herrick⁷¹ was led to believe from his personal observations that the occurrence of high blood pressure and increased concentration of glucose in the blood is present in a definite group of cases characterized by four cardinal symptoms: hypertension, hyperglycemia, obesity and arteriosclerosis. Mohler⁷² studied 46 patients varying in age from 30 years to 70 years with glycosuria and a blood pressure of 150 or more. Forty-five of the 46 patients ranged from 1 to 60 per cent overweight at the time of the observation, 36 of these weighing more than 200 pounds at some period of life. In 16 of these 36 patients, diabetes had developed. Mohler³ concluded that obesity frequently is a factor in the development

of sclerotic changes in the body which are capable of producing an increase in the blood pressure and a diminished ability of the body cells to utilize carbohydrate. Interesting are the studies of Hoppe-Seyler⁸⁴ and Herxheimer⁸⁵ who pointed out that in cases in which arteriosclerosis of the kidneys and hypertension are present, diabetes begins through an analogous arteriosclerosis of the pancreas. To this observation Wiechmann⁹⁶ added that a certain natural weakness of the pancreas may be a causative factor.

Tachau⁷⁴ and Harle³⁶ both found blood sugar values in nephritis with hypertension at the upper limits of the normal. In hypertension without clinically recognizable renal changes or other complications they found not only high blood sugar values but often definite hyperglycemia. Hitzengerber and Richter-Quittner²² found hyperglycemia present in all cases of vascular hypertension. Frank,⁶⁹ Billigheimer,⁸⁶ Kahler,⁸⁷ Petró,⁸⁸ Peiser,⁸⁹ Voegelin,⁹⁰ always found normal blood sugar values in hypertension or at least values that lie at the upper limits of normal.

In table 6 I have summarized the average blood sugar values given by seven different authors, these all fall within normal levels. In table 7 I have summarized further the conclusions of all the authors cited in this section on the relation of hypertension to hyperglycemia. Archer,² who studied a series of 20 typical cases of arthritis of the menopause, found in 70 per cent a diminished sugar tolerance in contrast to only 15 per cent in a parallel series of infectious cases. Of these 70 per cent of diminished sugar tolerance, 71 per cent had an associated hypertension or obesity or both.

TABLE 6
Average Blood Sugar Values in Hypertension (As Reported by Various Authors)

AUTHOR	YEAR	AVERAGE BLOOD SUGAR VALUE
Ryser ⁹² (Compiled from authors)	1916	87
Gettler and Backer ⁹³ (Compiled from 12 authors)	1916	91
Epstein and Aschner ⁹⁴	1916	96
Staub ⁹⁵	1921	96
Wiechmann ⁹¹	1924	96
von Noorden ⁷⁸	1927	85
Wiechmann ⁹⁶	1928	114

TABLE 7
Opinion of Authors on Hyperglycemia in Hypertension

AUTHOR	YEAR	NORMAL	INCREASED
Frank ⁶⁹	1911	*	
Billigheimer ⁸⁶	1921	*	
Kahler ⁸⁷	1922	*	
Petrén ⁸⁸	1927	*	
Peiser ⁸⁹	1927	*	
Voegelin ⁹⁰	1927		
Wiechmann ⁹¹	1924	*	*
von Noorden ⁷⁸	1927	*	
Ryser ⁹²	1916	*	
Gettler and Backer ⁹³	1916	*	
Epstein and Aschner ⁹⁴	1916	*	
Staub ⁹⁵	1921	*	
Wiechmann ⁹⁶	1928	*	*
Neubauer ⁷⁶	1910		*
O'Hare ⁷⁰	1920		*
Pearce and Keith ⁷⁷			*
Mohler ⁷²	1925		*
Seyler ⁸⁴	1904		*
Herxheimer ⁸⁵	1927		*
Tachau ⁷⁴	1911	*	
Harle ³⁶	1921	*	
Hitzenberger et al ²²	1921		*
Myers and Killian ⁷³		*	
Kylin ⁸	1921		*
Herrick ⁷¹	1923	*	*
		16	12

Table 8 presents the summary of my own observations of 50 uncomplicated cases of hypertension, based on glucose tolerance tests, and classified according to decades. It will be seen that in the earlier decades the incidence of diabetic curves is zero, whereas in the fifth decade and up the diabetic incidence rises rapidly. This fact is also demonstrated in chart VI which shows

the rapidly increasing incidence with advanced years. This observation is in line with the pathological observations of Herxheimer,⁸⁵ Fahr,⁹⁷ Aschoff,⁹⁸ Seyfarth,⁹⁹ and others who have shown that in hypertension, it is not only the renal arterioles which are affected first and most but the pancreas also shows changes of arteriosclerosis when the arterioles of the rest of the body

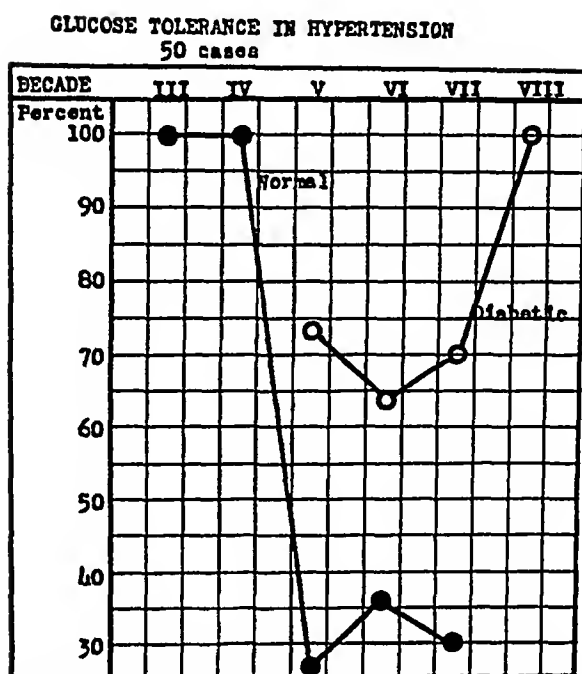


CHART VI Glucose tolerance in 50 cases of hypertension

TABLE 8
Analysis of Fifty Glucose Tolerance Tests in Hypertension According to Decades (John)

DECADE	NORMAL CURVES	PER CENT	DIABETIC CURVES	PER CENT
III	2	100		
IV	7	100		
V	4	27	11	73
VI	5	36	9	64
VII	3	30	7	70
VIII			2	100
Total	21	42	29	58

are not affected with any regularity Herxheimer pointed out that in cases in which arteriosclerosis of the kidneys and high blood pressure are present, the pancreatic blood vessel changes and the resultant changes in the islands are secondary Fraenkel¹⁰⁰ stated "These changes [pancreas, especially the cells of the islands] will be found in such boundaries as the various pathological changes of the blood vessels, from the beginning of the spasm, then through the angioneurosis on up to arteriosclerosis" Wiechmann⁹⁹ clearly stated

"Just as nephrocirrhosis arteriosclerotic can be the cause for increased blood pressure, so can the cirrhosis arteriosclerotic of the pancreas (Herxheimer) be the cause for the changes of the carbohydrate metabolism We must also note that often we are dealing only with functional changes which lead to similar clinical results as morphological changes Just as the high blood pressure can be but functional, so also do we find functional changes in the blood vessels of the pancreas which lead to hyperglycemia

and other changes in the carbohydrate metabolism ”

In my series of 50 cases of hypertension, glycosuria was present in 18 cases or 36 per cent (See table 9) Glycosuria was present six times in the presence of normal glucose tolerance curves (39 per cent), and it was absent sixteen times in diabetic curves (55 per cent) This leads us to the evaluation of the renal threshold which can be estimated fairly closely from a

ades Also one finds in cases of hypertension changes in blood sugar which are characteristic of diabetes mellitus The type of hypertension is the same in both and whether we are dealing with a functional hypertension or an anatomic hypertension the blood sugar pictures in both are similar

Many of the workers in this field look upon these changes in a large number of cases of hypertension as a latent diabetes,^{4, 85, 91 97, 98, 99} a predi-

TABLE 9
Glycosuria in Fifty Cases of Hypertension (John)

GLUCOSE TOLERANCE CURVE	GLYCOSURIA	PER CENT	NO GLYCOSURIA	PER CENT
Normal	6	39	15	71
Diabetic	13	45	16	55

	NO CASES	DIABETIC PER CENT	NON-DIABETIC PER CENT
Glycosuria	19	66	33
No Glycosuria	31	52	48

glucose tolerance test Table 10 shows that 47 per cent of these cases have a renal threshold above 180, which is high In my previous publication¹⁰¹ the average renal threshold for hypertension cases was also high, namely 165 (The average ranges were from 110 to 216)

TABLE 10 Renal Threshold in Hypertension (John)	
Below 140 mg /100 c c	23%
141 to 180 mg /100 c c	30%
181 to 200 mg /100 c c	33%
201 to 250 mg /100 c c	14%

From the previous consideration, then, it seems that there is a close connection between hypertension and hyperglycemia which in turn means diabetes either functional or anatomic Hypertension occurs more frequently in diabetics, especially in the later dec-

abetic stage A prediabetic stage does not necessarily come to the foreground and develop into a full fledged diabetes I have various groups of cases of latent diabetes and I keep them in this stage merely by a slight regulation of their diet, by a close observation of their weight, and by seeing that these patients get plenty of exercise There are also many observations of the opposite nature, namely—a prediabetic stage—a disregard of any diet—the development of obesity—diabetes This is a natural sequence in the evolution of diabetes in such a group Many of these cases of hypertension also die early which is another factor in eliminating a certain number of diabetics from our records

THE RELATION OF OVERWEIGHT AND UNDERWEIGHT TO BLOOD PRESSURE IN DIABETES MELLITUS AND DIABETES WITH HYPERTHYROIDISM

This study is based on observations of a total of 1,051 cases. Of these, 614 were cases of diabetes mellitus (292 male and 322 female) and 186 were cases of diabetes with hyperthyroidism (46 male and 140 female). A brief summary of the rise of blood pressure incidence reported by various authors can be gleaned from table 11. Tables 12 and 13 show a detailed analysis of these two groups of cases which I am reporting classified according to per cent of overweight, the increase in blood pressure and the distribution of male and female cases. Table 14 presents a similar analysis of the cases of underweight (in this group are included normal weights, up to plus 10 per cent above normal, and all cases below normal), cases of diabetes and cases of diabetes with hyperthyroidism. The data offered in table 12 are graphically expressed in chart VII in which it is clearly shown that in 50 per cent

of the cases of diabetes the blood pressure is above 140, and in 50 per cent the blood pressure is below 140. With increase in weight there is a decided increase in blood pressure. The data offered in table 13 (Diabetes and Hyperthyroidism) are graphically expressed in chart VIII. Here we find that in 66 per cent of these cases the blood pressure is above 140 and in only 34 per cent is the blood pressure below 140. Here we do not find the orderly sequence of increase in blood pressure with increase of weight, for other factors in addition to overweight enter into this picture.

Table 15 presents a detailed comparative analysis of blood pressure studies in overweight and underweight. These data are graphically expressed in chart IX which shows the increasing incidence of high blood pressure in per cent in overweight diabetics and a similar, although not as marked, increase in the incidence of high blood pressure in the presence of diabetes associated with hyperthyroidism.

Chart X presents a general summary

TABLE 11
Blood Pressure in Diabetes According to Various Authors

AUTHOR	AGE	BLOOD PRESSURE	PER CENT
von Noorden and Isaac ⁷⁸	1-50	above 140	30
	51-90	above 140	65
Kyllin ⁸	40-90	above 140	88
	40-90	above 160	72
	40-90	above 180	48
Hitzenberger ⁸⁰	40-90	above 140	64
	40-90	above 180	33
Joslin ⁸¹	21-50	above 150	58
	51-90	above 150	68
Kramer ¹¹ 500 cases	to 30	above 140	46
	31-80	above 140	51
John (present publ) 1385 cases	to 30	above 140	9
	31-90	above 140	49

TABLE 12
Relation of Overweight to Various Levels of Blood Pressure in Diabetes (John)

BLOOD PRESSURE		120	140	160	180	200	220	240	260	280	300	TOTAL	INCIDENCE PER CENT	
													BELOW 140	ABOVE 140
Overweight Per cent 10	male	30	19	16	5	3	1	1				75		
	female	19	14	12	3	4	2	1	1			56		
	Total	49	33	28	8	7	3	2	1			131	63	37
20	male	26	15	8	9	4	1					63		
	female	7	11	9	5	3	5					40		
	Total	33	26	17	14	7	6					103	57	43
30	male	21	20	11	3	2						57		
	female	8	18	12	6	10	2	1		2		59		
	Total	29	38	23	9	12	2	1		2		116	58	42
40	male	8	11	11	4	2	3					39		
	female	4	13	17	6	7	2	1			1	51		
	Total	12	24	28	10	9	5	1			1	90	40	60
50	male	10	6	7	1	5	1		1			31		
	female	3	8	15	10	7	2		1	1		47		
	Total	13	14	22	11	12	3		2	1		78	35	65
60	male	4	1	3	3	1		1				13		
	female	1	4	7	2	4	1					19		
	Total	5	5	10	5	5	1	1				32	31	69
70	male		3	1								4		
	female	5	3	10	5	2	1	1				27		
	Total	5	6	11	5	2	1	1				31	35	65
80	male	2	1	2	1							6		
	female	3	1	3		1	2					10		
	Total	5	2	5	1	1	2					16	43	57
90	male		1	1	1		1					4		
	female		4	6	2	1						13		
	Total		5	7	3	1	1					17	29	71
Grand total		151	153	151	66	56	24	6	3	3	1	614	495	505

TABLE 13
Relation of Overweight to Various Levels of Blood Pressure in Diabetes with
Hyperthyroidism (John)

BLOOD PRESSURE		120	140	160	180	200	220	240	TOTAL	INCIDENCE PER CENT	
										BELOW 140	ABOVE 140
Overweight Per cent 10	male		7	8	4				19		
	female	3	11	11	7	2	3	2	39		
	Total	3	18	19	11	2	3	2	58	36	74
20	male	5	3		4	3	3	1	8		
	female	5	3	6	4	3	3	1	25		
	Total	10	6	6	4	3	3	1	33	48	52
30	male	2	2	3	1	2			10		
	female	2	3	7	9	4	1		26		
	Total	4	5	10	10	6	1		36	25	75
40	male	1	1	1					3		
	female	2	4	4	5	4	2		21		
	Total	3	5	5	5	4	2		24	33	67
50	male		1	3	1				5		
	female	1	3	10	4	1			19		
	Total	1	4	13	5	1			24	20	80
60	male			1					1		
	female		2	1		1	1		5		
	Total		2	2		1	1		6	33	67
70	male				1				0		
	female		1						2		
	Total		1		1				2	50	50
80	male								0		
	female						1		1		
	Total						1		1	0	100
90	male								0		
	female	2							2		
	Total	2							2	100	0
Grand total		21	43	55	36	17	11	3	186	343	657

DIABETES

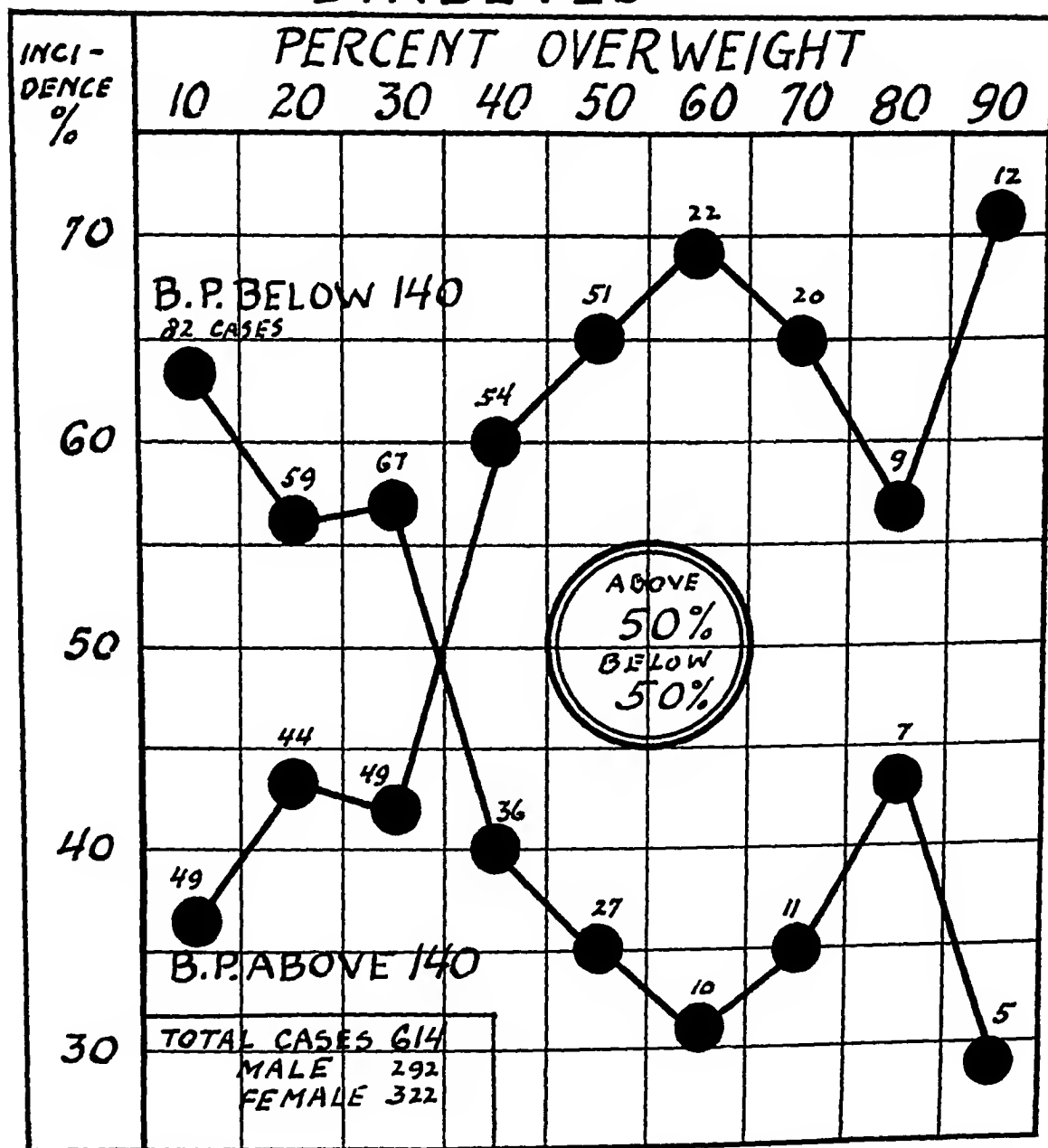


CHART VII The relation of per cent of overweight to rise in blood pressure in diabetes

of the relationship of overweight and underweight to hypertension, that is, a good pressure below and above 140 mm in diabetes and in diabetes with hyperthyroidism. In both conditions there is a definite increase in the incidence of hypertension in cases presenting overweight, and a definite decrease in the incidence of hypertension, which is most marked in uncomplicated diabetes, in cases of normal weight or underweight.

SUMMARY

1 Blood pressure in non-diabetics rises proportionately higher in the case of obese individuals than in those of normal weight (approximately 12 per cent increase)

2 Reduction in weight in non-diabetics brings about reduction in blood pressure

3 The consensus of opinion of various authors is that the blood pressure is higher in diabetics than in normal

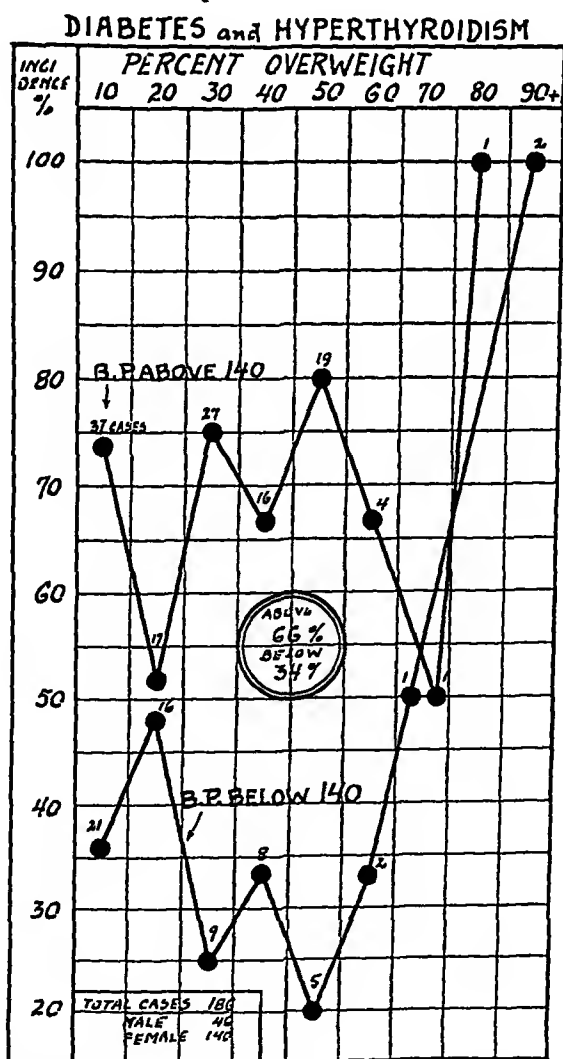


CHART VIII The relation of per cent of overweight to blood pressure in diabetes and hyperthyroidism

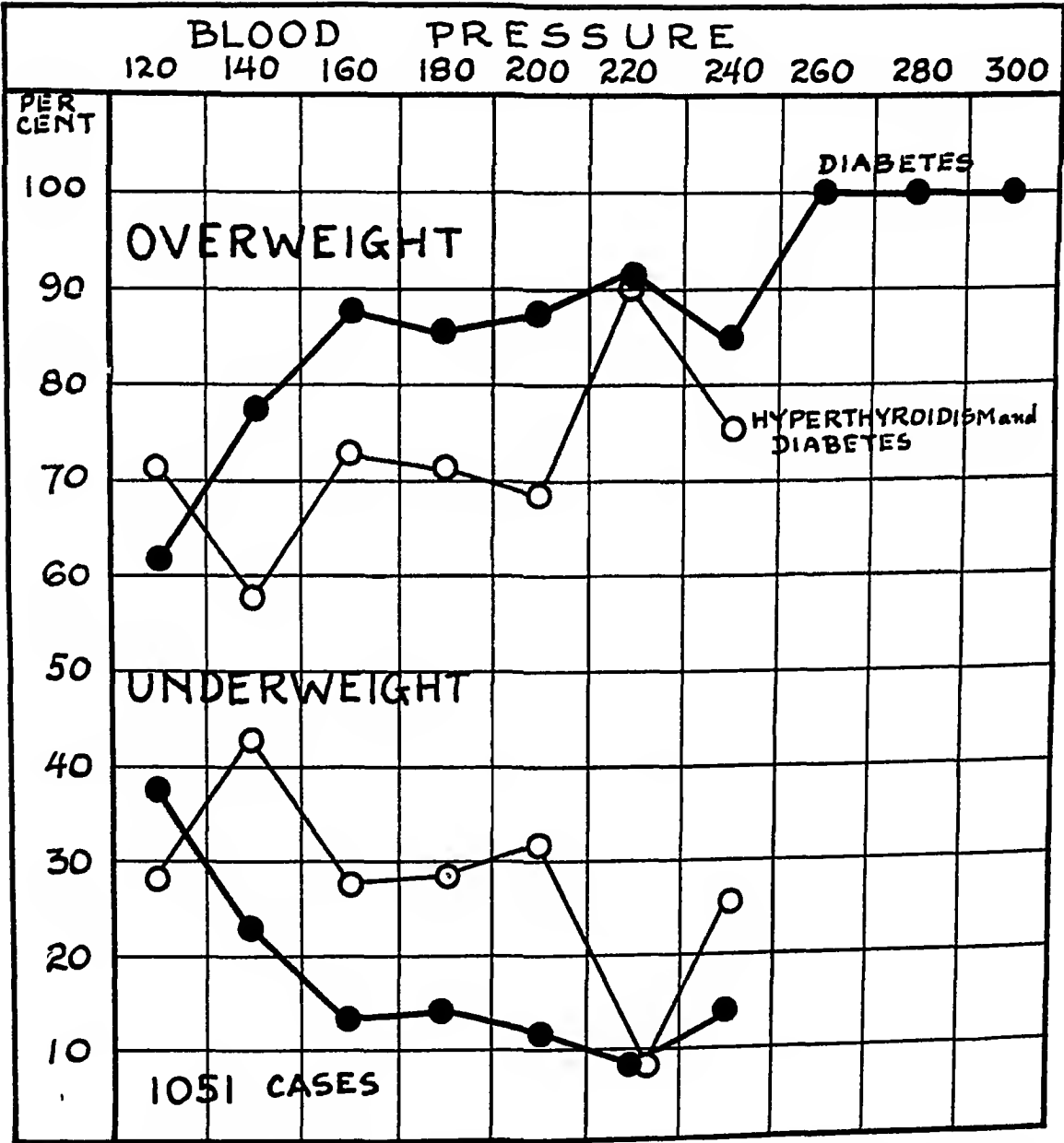


CHART IX The comparative relationship of overweight, underweight, to the blood pressure incidence in diabetes and diabetes with hyperthyroidism

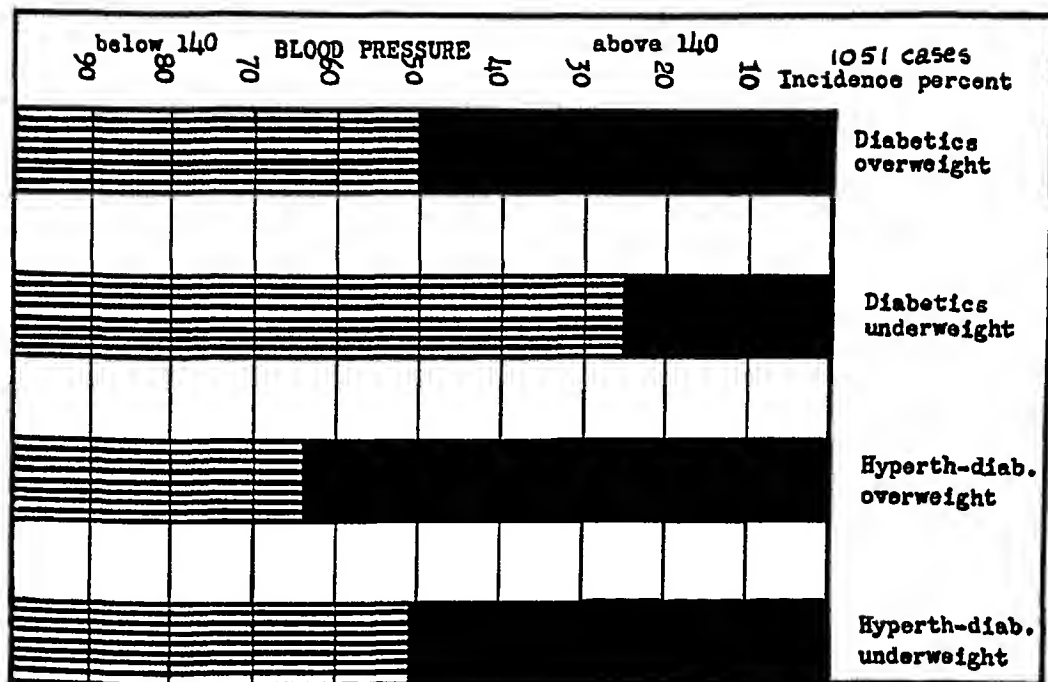


CHART X A summary of an analysis of the relationship of underweight and overweight to blood pressure level classified below and above 140 mm in diabetes and in diabetes with hyperthyroidism

individuals of the same age. In my own series of 1828 cases of diabetes the blood pressure was the same as in normals below and including the fourth decade, above this age the incidence of high blood pressure was greater in diabetics.

4 In my series of 443 cases of diabetes associated with hyperthyroidism 37.6 per cent of the patients had a blood pressure below 140 mm and 62.4 per cent had a blood pressure above 140 mm against 54.3 and 45.7 per cent respectively in diabetes not associated with hyperthyroidism.

5 In my series of cases the diabetics up to 30 years of age showed hypertension only in 9 per cent whereas in diabetics with hyperthyroidism, hypertension was present in 42 per cent of

this group of young individuals. Up to the fifth decade, hypertension in itself presents no marked incidence of diabetes, after the fifth decade the incidence rises markedly.

6 In 50 cases of hypertension in my series, glycosuria was present in 36 per cent. In 50 glucose tolerance tests on these individuals, 39 per cent showed glycosuria in the presence of a normal curve and 55 per cent showed no glycosuria in the presence of a diabetic curve.

7 The renal threshold in cases of hypertension is high.

8 A close relationship exists between hypertension and diabetes, and hypertension occurs more frequently in diabetics than in non-diabetics.

TABLE 14

Summary of All Underweight* Patients in Relation to Blood Pressure (John)

BLOOD PRESSURE			120	140	160	180	200	220	240	TOTAL	INCIDENCE PER CENT	
											BELOW 140	ABOVE 140
DIABETES	Under-weight Per cent 10	male female	27 16	20 9	7 8	4 2	3 3	1 1	1	63 39		
		Total	43	29	15	6	6	2	1	102	71	29
	20	male female	13 11	7 6	3 1	3 1	1 1			27 20		
		Total	24	13	4	4	2			47	79	21
	30	male female	9 9		1 1	1				10 14		
		Total	18	3	2	1				24	87	13
	40	male female	1 3							1 3		
		Total	4							4	100	0
	Grand Total		89	45	21	11	8	2	1	177	75	25

DIABETES WITH HYPERTHYROIDISM	10	male female	1 4	10 8	4 9	6 6	5 5		1	15 33		
		Total	5	18	13	6	5		1	48	48	52
	20	male female	1 1	4 7	2 3	2 5	3 3	1		8 20		
		Total	1	11	5	7	3	1		28	43	57
	30	male female	2 2	2 2	2 1	1				0 7		
		Total	2	2	2	1				7	57	43
	40	male female		1						0 1		
		Total		1						1	100	0
	Grand Total		8	32	20	14	8	1	1	84	47	53

*In underweight I have classified actual underweight, normal weight and up to ten per cent above normal weight throughout the paper

TABLE 15
Comparative Study of Overweight and Underweight in 1051 Cases With Their
Respective Relation to Blood Pressure (John)

BLOOD PRESSURE			120	140	160	180	200	220	240	260	280	300	TOTAL	%
OVERWEIGHT	Diabetes	male	101	77	60	27	17	7	2	1			292	
		female	50	76	81	39	39	17	4	2	3	1	312	
		Total	151	153	141	66	56	24	6	3	3	1	604	
	Diabetes Hyperth	male	8	14	16	6	2						46	
		female	13	29	39	30	15	11	3				140	
		Total	21	43	55	36	17	11	3				186	
	Grand Total		172	196	196	102	73	35	9	3	3	1	790	75.1
UNDERWEIGHT	Diabetes	male	50	27	11	7	4	1	1				101	
		female	39	18	10	4	4	1					76	
		Total	89	45	21	11	8	2	1				177	
	Diabetes Hyperth	male	1	14	6	2							23	
		female	7	18	14	12	8	1	1				61	
		Total	8	32	20	14	8	1	1				84	
	Grand Total		97	77	41	25	16	3	2				261	24.9
ALL CASES	Per cent overweight		63.9	72	83	80	82	92	82	100	100	100		
	Per cent underweight		36.1	28	17	20	18	8	18	0	0	0		

REFERENCES

- ¹RISMAN, J. E. F., and WEISS, S. The age and sex incidence of arterial hypertension, *Am Heart Jr*, 1929, v, 172-190
- ²HARTMAN, H. R. and CHRIST, D. G. Blood pressure and weight, *Arch Int Med*, 1929, xlv, 877-881
- ³MOHLER, H. K. Hypertension and hyperglycemia, *Jr Am Med Assoc*, 1925, lxxxiv, 243-245
- ⁴WILCHMANN, E. Die Entstehungsbedingungen der Zuckerkrankheit, *Munch med Wchnsch*, 1929, lxxvi, 98-101
- ⁵ADAMS, S. A study of the blood pressure of patients with diabetes mellitus, *Am Jr Med Sci*, 1929, clxxvii, 195-201
- ⁶KOOPMAN, J. Blood pressure and sugar metabolism, *Endocrinology*, 1924, viii, 340-346
- ⁷HITZENBERGER, K. Über den Blutdruck bei Diabetes mellitus, *Wien Arch f inn Med*, 1921, ii, 461
- ⁸KYLIN, E. Hypertonie und Zuckerkrankheit, *Zentralbl f inn Med*, 1921, xlii, 873-877
- ⁹KATZ-KLEIN, F. Diabetes und Hypertonie, *Med Klinik*, 1924, ii, 1808-1811
- ¹⁰PETERSON, R. F. The relation of hypertension and arteriosclerosis to diabetes mellitus (Unpublished thesis, cited by Adams,⁵ 1929)
- ¹¹KRAMER, D. W. Hypertension and diabetes, *Am Jr Med Sci*, 1928, clxxvi, 23-31
- ¹²ROSENBLOOM, J. Blood pressure studies in one hundred and forty cases of diabetes mellitus, *Jr Lab and Clin Med*, 1922, vii, 392-399
- ¹³ELLIOTT, A. R. A clinical study of blood pressure variations in diabetes and their bearing on the cardiac complications, *Jr Am Med Assoc*, 1907, xlix, 27-30
- ¹⁴FABER, H. K. A formula expressing a general relationship between pressure and body weight, *Proc Soc Exper Biol Med*, 1927, xxv, 77-80
- ¹⁵SYMONDS, B. The blood pressure of healthy men and women, *Jr Am Med Assoc*, 1923, lxxx, 232-236
- ¹⁶HUBER, E. G. Systolic blood pressure

- of healthy adults in relation to body weight, *Jr Am Med Assoc*, 1927, lxxxviii, 1554-1557
- ¹⁷TERRY, A H Jr Obesity and hypertension, *Jr Am Med Assoc*, 1923, lxxx, 1283-1284
- ¹⁸ROSE, R H Weight reduction and its remarkable effect on high blood pressure, *New York Med Jr*, 1922, cxv, 752-755
- ¹⁹JOHN, H J The relation of weight to diabetes, *Endocrinology*, 1930, xiv, 282-287
- ²⁰LARSEN, V [Diabetes and hypertension], *Ugesk f Laeger*, 1929, xci, 695
- ²¹MARAÑÓN, G Hipertensión y diabetes, *Arch cardiol y hemat*, 1922, iii, 125-131
- ²²HIRZENBERGER, K, and RICHTER-QUITNER, M Ein Beitrag zum Stoffwechsel bei der vaskulären Hypertonie, *Wien Arch f inn Med*, 1921, ii, 189-232
- ²³KYLIN, E High blood pressure and diabetes, *Hygeia*, 1922, lxxxiv, 49-56
- ²⁴JOSLIN, E P Arteriosclerosis and diabetes, *Ann Clin Med*, 1927, v, 1061-1141
- ²⁵THOMAS, E Recherches expérimentales touchant l'influence de la cholestérine sur le développement de l'hypertension artérielle, *Arch d mal du coeur*, 1926, xix, 641-646
- ²⁶LETULLE, M, LABBÉ, M, and HERTZ, J De la calcification des arteres chez les diabetiques, *Arch d mal du coeur*, 1927, xx, 577-597
- ²⁷FABER, A [Arteriosclerosis, calcification of vessels in man and animals], *Ugesk f Laeger*, 1926, lxxxviii, 433-438
- ²⁸EDITORIAL Blood peptids and arterial hypertension, *Jr Am Med Assoc*, 1927, lxxxix, 970
- ²⁹SHAPIRO, S Relation of certain glands of internal secretion to development of arteriosclerosis, *Endocrinology*, 1927, xi, 279-289
- ³⁰EDITORIAL The pathogenesis of hypertension, a new theory, *Jr Am Med Assoc*, 1926, lxxxvii, 248
- ³¹STRISOWER, R Insulin und Blutdruck, *Wien Arch f inn Med*, 1927, xiv 429-434
- ³²HAHN, L [Diphasic action of insulin on blood pressure], *Klin Wchnschr*, 1926, v, 1429
- ³³BREMS, A, and HOLTEN, C [Rise of blood pressure in certain so-called hyperglycemic cases after insulin injections], *Bibliot f Laeger*, 1929, clxxx, 463-482
- ³⁴HERRICK, W W Hyperglycemia and hypertension, *Jr Am Med Assoc*, 1923, lxxx, 1942-1944
- ³⁵KAHN, M Angina pectoris of diabetes, *Jr Am Med Assoc*, 1921, lxxvi, 570
- ³⁶HÄRLE, F Hypertonie und Blutzucker, *Ztschr f klin Med*, 1921, xcii, 124-133
- ³⁷WIECHMANN, E Hypertension und Blutzucker, *Deutsch, Arch f klin Med*, 1928, clxi, 92-110
- ³⁸BORDLEY, J, III, and BAKER, B M, JR A consideration of arteriosclerosis of the cerebral vessels and the pathogenesis of hypertension, *Bull Johns Hopkins Hosp*, 1926, xxxix, 229-264
- ³⁹ANREP, G V, and STARLING, E H Central and reflex regulation of circulation, *Proc Roy Soc*, 1924-1925, xcvi, Ser B, 463-487
- ⁴⁰STARLING, E H . The physiologic factors in hyperplasia, *Brit Med Jr*, 1925, ii, 1163-1165
- ⁴¹GIBBES, J H Analysis of one hundred cases of hypertension, *South Med Jr*, 1926, xix, 413-416
- ⁴²BARACH, J H Essential vascular hypertension, *Jr Am Med Assoc*, 1922, lxxix, 2140-2143
- ⁴³THOM, B P Syphilis and high blood pressure, *Med Rec*, 1922, ci, 89-93
- ⁴⁴DAVIS, N S Arterial hypertension; its relationship to chronic intestinal disorders, *Med Clin N Am*, 1923, vii, 547-553
- ⁴⁵NEWBURGH, L H, and CLARKSON, S Renal injury produced in rabbits on diets containing meat, *Arch Int Med*, 1923, xxxii, 850-869
- ⁴⁶NUZUM, F R OSBORNE, M, and SAN-SUM, W D Experimental production of hypertension, *Arch Int Med*, 1925, xxxv, 492-499
- ⁴⁷MCCOLLUM, S V, POLVOGT, L M, and SIMMONDS, N Production of kidney lesions in rats by diets defective only in

- that they contain excessive amounts of proteins, *Bull Johns Hopkins Hosp*, 1923, *xxiv*, 168-172
- ⁴⁸MAJOR, R H Cause and treatment of arterial hypertension, *Jr Kansas Med Soc*, 1925, *xxv*, 177-179
- ⁴⁹MAJOR, R H Excretion of guanidine bases in two cases of arterial hypertension with reduction in blood pressure, *Bull Johns Hopkins Hosp*, 1925, *xxvi*, 357-360
- ⁵⁰MAJOR, R H Effects of hepatic extract on high blood pressure, *Jr Am Med Assoc*, 1925, *lxxxv*, 251-253
- ⁵¹MACDONALD, W J Extractives of liver possessing blood pressure reducing properties, *Canad Med Assoc Jr*, 1925, *xv*, 697-701
- ⁵²JAMES, A A, and LAUGHTON, N B Control of blood pressure with liver extracts, *Canad Med Assoc Jr*, 1925, *xv*, 701-702
- ⁵³OLIVER, G, and SCHAFER, E A On the physiological action of extracts of pituitary body and certain other glandular organs, *Jr Physiol*, 1895, *xviii*, 277-279
- ⁵⁴EDITORIAL Lowering the blood pressure with liver extract, *Jr Am Med Assoc*, 1925, *lxxxv*, 194-195
- ⁵⁵MAJOR, R H Relationship between certain products of metabolism and arterial hypertension, *Jr Am Med Assoc*, 1924, *lxxxiii*, 81-84
- ⁵⁶DALE, H H, and DIXON, W E The action of pressure amines produced by putrefaction, *Jr Physiol*, 1909, *xxxix*, 25-44
- ⁵⁷BARGER, G, and DALE, H B B-mitazolyethylamine, a depressor constituent of intestinal mucosa, *Jr Physiol*, 1910-1911, *xli*, 499-503
- ⁵⁸HARVEY, W H Auto-intoxication and experimental nephritis in rabbits, *Jr Path and Bact*, 1912, *xvi*, 95-105
- ⁵⁹CLARK, A The clinical application of ergotamine (tyramine), *Jr Biochem*, 1910, *v*, 236-242
- ⁶⁰WESTPHAL, K Untersuchungen zur Frage der Entstehungsbedingungen des genuinen arteriellen Hochdruckes, *Ztsch f klin Med*, 1925, *ci*, 545-557
- ⁶¹REID, W D Arterial hypertension, *Boston Med and Surg Jr*, 1925, *cxcii*, 883-890
- ⁶²KYLIN, E Über die Einwirkung der Ca und K-ionen auf Pituitrin-Blutzucker-Reaktion, *Klin Wchschr*, 1925, *iv*, 2068
- ⁶³POST, W E, and STIEGLITZ, E J Hypertension, clinical aspects of etiology and therapy, *Am Jr Med Sci*, 1926, *clxxi*, 648-654
- ⁶⁴SCHMIDTMANN, M Experimentelle Studien zur Pathogenese der Arteriosclerose, *Virchow's Arch f path Anat*, 1922, *ccxxxvii*, 1-21
- ⁶⁵ANITSCHKOW, N Über die experimentelle Atherosklerose der Aorta beim Meerschweinchen, *Beitr z path Anat u, allg Path*, 1922, *lxx*, 265-281
- ⁶⁶MONCKFBERG, J C Arteriosklerose, *Klin Wchschr*, 1924, *iii*, 1473-1478
- ⁶⁷SCHONHEIMER, R Über die experimentelle Cholesterin krankheit der Kaninchen, *Virchows Arch f path Anat*, 1924, *ccxlix*, 1-42
- ⁶⁸NUZUM, F R, SEEGAR, B, GARLAND, R, and OSBORNE, M Arteriosclerosis and increased blood pressure, *Arch Int Med*, 1926, *xxxvii*, 733-744
- ⁶⁹FRANK, E 1 Bestehen Beziehungen zwischen chromaffinem Hypertonie des Menschen? 2 Ein kritischer Beitrag zu der Lehre von der physio-pathologisch 3 Bedeutung des Adrenalins, *Deutsch Arch f klin Med*, 1911, *ciii*, 397-412
- ⁷⁰O'HARE, J P Glucose tolerance test in chronic vascular hypertension, *Am Jr Med Sci*, 1920, *clx*, 366
- ⁷¹HERRICK, W W Hypertension and hyperglycemia, *Jr Am Med Assoc*, 1923, *lxxxi*, 1942-1944
- ⁷²MOHLER, H K Hypertension and hyperglycemia, observations on a series of 46 cases, *Jr Am Med Assoc*, 1925, *lxxxiv*, 243-245
- ⁷³MEYERS, V C, and KILLIAN, J A Studies in animal diastasis, the increased diastatic activity of the blood in diabetes and nephritis, *Jr Biol Chem*, 1917, *xxix*, 179-189
- ⁷⁴TACHAU, H Eine neue Methode der Bestimmung des Blutzuckergehaltes,

- Deutsch Arch f klin Med, 1911, cii, 597-605
- ⁷⁵PEISER, F Über den hypertonen Diabetes, Klin Wchnschr, 1927, vi, 1419-1423
- ⁷⁶NEUBAUER, E Über Hyperglykämie bei Hochdrucknephritis und die Beziehungen zwischen Glykämie und Glykosurie beim Diabetes mellitus, Biochem Ztschr, 1910, xxv, 284-295
- ⁷⁷PEARCE and KEITH Personal communication
- ⁷⁸VON NOORDEN, C H, and ISAAC, S Die Zuckerkrankheit und ihre Behandlung, 1927 Julius Springer, Berlin
- ⁷⁹MARAÑON, G Über Hypertonie und Zuckerkrankheit, Zentralbl f inn Med, 1922, xliii, 169-176
- ⁸⁰HITZENBERGER, K Über den Blutdruck bei Diabetes mellitus, Wien Arch f inn Med, 1921, ii, 461-466
- ⁸¹JOSLIN, E P The treatment of diabetes mellitus, 1928, Lea and Febiger, Philadelphia
- ⁸²JANEWAY, T C Important contributions to clinical medicine during the past thirty years from the studies of human blood pressure, Johns Hopkins Hosp Bull, 1915, xxvi, 341-350
- ⁸³ELLIOTT, A R A clinical study of blood pressure variations in diabetes and their bearing on the cardiac complications, Jr Am Med Assoc, 1907, xlix, 27-30
- ⁸⁴HOPPE-SEYLER, G Beitrag zur Kenntniss der Beziehungen der Erkrankung des Pankreas und seiner Gefasse zum Diabetes mellitus, Deutsch Arch f klin Med, 1894, lii, 171-177 Über chronische Veränderungen des Pankreas bei Arteriosklerose und ihre Beziehung zum Diabetes mellitus, Deutsch Arch f klin Med, 1904, lxxxii, 119-162
- ⁸⁵HERXHEIMER, G Pankreas, Handbuch d inn Sekretion, ed M Hirsch, 1927, Curt Kabitzsch, Leipzig, i, 25-122
- ⁸⁶BILLIGHEIMER, E Über die Wirkungsweise der probatorischen Adrenalininjektion, Deutsch Arch f klin Med, 1921, cxxxvi, 1-32
- ⁸⁷KAHLER, H Zur Frage der Hyperglykämie bei Krankheitszuständen mit Hochdruck, Wien Arch f inn Med, 1922, iv, 129-148
- ⁸⁸PETREN Cited by von Noorden and Isaac (1 c 78)
- ⁸⁹PEISER, F Über die Blutzuckeruberttrittsschwelle bei Hypertonikern mit und ohne Diabetes, Ztschr f klin Med, 1927, cvi, 290-309
- ⁹⁰VOEGELIN, H Über die Beziehung der Hypertonie zur Hyperglykämie, Deutsch Arch f klin Med, 1927, clvi, 178-181
- ⁹¹WIECHMANN, E Zur Frage der Permeabilität der roten Blutkörperchen für Traubenzucker unter Besonderen Berücksichtigung des Diabetes, Ztschr f d ges exper Med, 1924, xli, 462-492
- ⁹²RYSER, H Der Blutzucker während der Schwangerschaft, der Geburt, im Wochenbett und bei den Schwangerschaftstoxikosen, Deutsch Arch f klin Med, 1916, cxviii, 408-461
- ⁹³GETTLER, A O, and BACKER, W Chemical and physical analysis of blood in thirty normal cases, Jr Biol Chem, 1916, xxv, 211-222
- ⁹⁴EPSTEIN, A A, and ASCHNER, P W The effect of surgical procedures on the blood sugar content, Jr Biol Chem, 1916, xxv, 151-162
- ⁹⁵STAUB, H Untersuchungen über den Zuckerstoffwechsel des Menschen, Ztschr f klin Med, 1921, xci, 44-60
- ⁹⁶WIECHMANN, E Hypertension und Blutzucker, Deutsch Arch f klin Med, 1928, clxi, 92-110
- ⁹⁷FAHR, T Experimentelle Beiträge zur Frage des Pankreas-diabetes, Verhandl d deutsch path Gellesch, 1913, xvi, 289-294
- ⁹⁸ASCHOFF, L (Cited by Herxheimer, 1 c 85)
- ⁹⁹SEYDARTH, C Neue Beiträge zur Kenntnis der Langerhans'schen Inseln im menschlichen Pankreas und ihre Beziehung zum Diabetes mellitus, 1920, G Fischer, Jena
- ¹⁰⁰FRAENKEL, M Die Bedeutung der Langerhans'schen Inseln in ihrer Stellung zum übrigen Pankreas-gewebe und ihre Beziehung zum Diabetes, Wurzb Abhandl a d Gesamtgeb d prak Med, 1908, viii, 269-290
- ¹⁰¹JOHN, H J A study of 1,100 glucose tolerance tests, Med Jr and Rec, 1930, cxxxii, 287-292, 351-354, 398-402
- ¹⁰²RIESMAN, D Hypertension in women, Jr Am Med Assoc, 1919, lxxiii, 330

The Fallacy of the Weighed Diet in the Treatment of Diabetes Mellitus*†

By HELMUTH ULRICH, M D , F A C P , *Boston, Massachusetts*

THE weighing of food is regarded as a great hardship by nearly all sufferers from diabetes mellitus, and I have become convinced that it is a burden they should not be required to bear. Hairsplitting figures concerning carbohydrate, protein and fat may make a fine appearance in a published article, but it is unlikely that they ever represent the actual conditions that obtain in the patient's kitchen. I am sure that the weighing of food is practiced much less than it is preached.

Weighed diets are prescribed because they are supposed to make possible an accurate computation of the nutritive value of the food that is eaten by the patient. In order that the expenditure of time and energy required for the process of weighing shall be warranted it is necessary to prove, (1) that the accuracy that is assumed to accrue is actually attained, (2) that the degree of accuracy, if achieved, is sufficiently great to pay for the effort, (3) that good results can not be obtained by a simpler method.

Concerning the first of these, the at-

tainment of accuracy, it may be natural to assume offhand that careful weighing of the food enables one to know exactly the amount of carbohydrate, protein and fat that is absorbed by the body and the number of calories derived therefrom, but it requires very little ingenuity to expose the fallacy of such an assumption. There are too many variables.

One of them is the process of digestion and absorption. It varies with different persons and in the same person at different times. Changing nervous and mental states, the varying activities of the gastrointestinal canal and its accessories, the effect of the composition of the diet on the rate and other phases of digestion, and probably many other known and unknown influences are involved.

The amount of cellulose in the diet, for example, is said to have a bearing on the utilization of protein and other foods. Also, slow absorption of a certain amount of carbohydrate, taken as slowly digested starch, appears to have less influence on the level of the blood sugar than rapid absorption of the same amount of carbohydrate taken as easily assimilated dextrose.

That is illustrated by table I which shows the difference between the changes of the level of blood sugar pro-

*From the Evans Memorial for Clinical Research and Preventive Medicine, Boston University School of Medicine, and The Massachusetts Memorial Hospitals, Boston.

†Received for publication, October 20, 1931.

duced in two fasting patients after the ingestion of 50 grams of dextrose and an equivalent amount, 250 grams, of boiled potato. In case I the blood sugar increased 86 per cent following dextrose and 50 per cent after the potato, in case II it increased 100 per cent after dextrose and only 50 per cent from the potato.

An important error in the process of weighing is introduced by the variable composition of items of food. Superficial study of any of the tables of food analyses will support this assertion.

Take the item of meat, for example. The much quoted tables by Atwater and Bryant¹ indicate, as shown in table II, that there are great variations in the composition of cooked beef.

Similar differences are found with other foods. The sugar in orange juice varies from 5.04 to 14.3 per cent,² the carbohydrate, exclusive of fiber, in the edible portion of carrots has a variation of from 5.9 to 11.5 per cent,* beets

*All data of analyses contained in this article are taken from Atwater and Bryant's tables, unless it is stated otherwise.

vary from 3.2 to 14.4 per cent and parsnips from 6 to 14.2 per cent. Even eggs, seemingly so uniform, vary in protein from 11.4 to 17.4 per cent, and in fat from 8.6 to 15.1 per cent.

Table III shows the variations that may occur in a day's ration designed by Joslin³ to contain 30 grams of carbohydrate, 48 grams of protein and 119 grams of fat. Theoretically it supplies 1,383 calories.

As a basis for constructing the table I have assumed the possibility that on certain days the ration may contain the minimal food values given for each item by Atwater and Bryant and others, and on other days the maximal values. For the estimation of the caloric value and its variation, however, I have combined the maximal amount of fat with the minimal amounts of protein and carbohydrate of each item, and vice versa, except in the case of fruits and vegetables. That is to say, a portion of meat with much fat usually contains a correspondingly small amount of protein, but fruits and vegetables that are high in protein are likely

TABLE I
Difference between the Changes of the Level of the Blood Sugar, in Milligrams per 100 c c
Following Ingestion of 50 Grams of Dextrose and 250 Grams of Boiled Potato

TIME	CASE 1		CASE 2	
	DEXTROSE	POTATO	DEXTROSE	POTATO
Before	307	334	200	148
1 hour	400	364	307	190
2 hours	571	444	363	222
3 hours	500	500	400	210
4 hours	400	444	307	190
5 hours	307	308	250	174
Rise in mg	264	166	200	74
Rise per cent	86	50	100	50

TABLE II
Variations in the Composition of Cooked Beef (Atwater and Bryant)

	PROTEIN	FAT	FUEL VALUE PER POUND
Roast Beef	14.5 — 29.7%	19.6 — 41.4%	1210 — 2030 Cal
Round Steak	20.3 — 34.1%	3.3 — 16.9%	615 — 1170 Cal
Loin Steak	20.6 — 26.6%	11.8 — 35.7%	925 — 1875 Cal

TABLE III
Variations That Are Possible with a Carefully Weighed Diet Planned to Contain 30 Grams of Carbohydrate, 48 Grams of Protein and 119 Grams of Fat

	GRAMS	CARBOHYDRATE		PROTEIN		FAT		CALORIES	
		MIN	MAX	MIN	MAX	MIN	MAX	MIN	MAX
Bacon ^a	30	0	0	19	54	75	15	89	143
Egg (one)		0	0	57	87	43	75	73	90
Chicken ^b	45	0	0	7	114	07	127	52	142
Meat ^c	45	0	0	68	153	15	341	75	334
40% cream ^d	150	22	45	31	33	60	63	571	588
Grapefruit ^e	200	92	17	06	12	02	04	41	76
Lettuce	50	06	19	03	09	01	03	5	14
5% vegetables	420	71	269	08	252	0	59	32	261
Butter ^f	30	0	0	01	1	233	261	214	235
Total		191	503	263	724	976	165	1151	1883

^aThe fat content of fried bacon is estimated. Accurate data are not available

^bIncluding fowl

^cCooked beef only. Satisfactory data for other cooked meats are not available. If other meats were included the variations would probably be greater.

^dPercentages of fat in 40% cream were supplied by H P Hood and Sons, Boston, percentages of carbohydrate and protein are from data supplied by Massachusetts State College and from Joslin.³ The figures given here apply to 40% cream only, if ordinary heavy cream were used the variation of fat would be much greater.

^eData for grapefruit are from Chatfield and McLaughlin.²

^fData for butter were supplied by Massachusetts State College.

to be high in carbohydrate, also. This adjustment makes the variations of the caloric values given on the table much less fanciful.

I readily grant that the grouping of all minimal or all maximal values on any one day must be looked upon as an academic possibility only. Usually the extremes will have a tendency to balance each other and form a more or less constant daily mixture. But that means that it is not the weighing but the law of chance that determines the relative uniformity of the diet. The same law would operate if a simpler method were used.

A majority of the foods have been analyzed in their raw state, but cooking has a profound influence on their composition. It removes much of the carbohydrate from vegetables and much fat from meats.

For an illustration let us take bacon. Smoked, uncooked bacon is listed as containing from 40 to 79.7 per cent fat, which in itself is a large variation,

amounting to a difference of about 90 calories in a serving of one ounce. Fried bacon (not listed by Atwater and Bryant) is assumed to contain about 40 per cent of fat by Campbell and Porter,⁴ and 50 per cent by Joslin³ and Huddleson.⁵ How closely this is approached depends on the degree of frying. Estimates based on the loss of weight resulting from the frying indicate that crisp bacon may contain as little as 25 per cent of fat and lightly fried bacon as much as 50 per cent. In regard to vegetables, von Noorden long ago called attention to the great loss of carbohydrate that was brought about by the process of cooking. He stated that raw spinach, for example, contains 2.97 per cent of carbohydrate, cooked spinach only 0.85 per cent.

Another uncertainty, a very important one, is introduced by the patients' inability or unwillingness to carry out orders. Intentionally or not they frequently break a set of rules or a dietetic prescription. The unintentional

violations may be eliminated by training, control of the wilful infractions is more difficult. I am convinced that a dietetic prescription that requires weighing of the food is broken more often than one that is carried out more easily. The order to weigh food, therefore, may defeat the very purpose for which it is given.

All this shows that accuracy can not be achieved by the use of the scales.

It may be argued that the weighing method, although admitted to be not wholly accurate, may nevertheless approach accuracy more closely than any other method. This must be conceded, at least in theory. It brings us to the consideration of the second and third postulates stated at the beginning, namely, that the degree of accuracy must be sufficient to pay for the effort, and that good results can not be obtained by a simpler method.

They may be considered together, because they are interdependent. If weighing of the food is the only method by which a reasonable degree of accuracy can be reached, then the scales must be used, but if a simpler method is nearly as accurate, then the expenditure of time and energy required for the process of weighing is not warranted.

When I began to treat diabetes I followed the prevalent custom of prescribing weighed diets, but I abandoned that method very soon. During the past ten years I have not asked one of my patients to follow it. I am using more easily understood household measures and natural food units in my dietetic prescriptions. The menu given in table IV is an example. The percentages of carbohydrate, protein and fat in this table are rough approxima-

tions only, but I am confident that they are nearly as accurate as if the food had been weighed with the utmost care.

This statement is supported by the results obtained with a group of patients who received an unweighed diet and whose level of the blood sugar was determined on several consecutive mornings before breakfast. A comparison of these results with others obtained with patients receiving a weighed diet showed no significant differences in regard to the daily variations of the blood sugar.

I am aware that dietetic prescriptions by weights and calories are easier for the physician. I use them constantly in the hospital where the services of a trained dietitian are available. Outside of the hospital, however, the burden of translating such a prescription into a day's menu is placed on the patient. A few patients have sufficient leisure, inclination and intelligence to do it in a satisfactory manner; many more have not. They should not be required to perform a task that properly belongs to the physician.

The many and changing systems of the dietetic treatment of diabetes give support to the thesis that burdensome attention to minute details is not necessary. Sansum⁶ prescribed high carbohydrate diets, Newburgh and Marsh⁷ advocated high fat diets, Allen depended on starvation, and all of us allow more carbohydrate now than we did in the past. Rabinowitch⁸ has recently emphasized again that slight undernutrition, stressed also by Allen⁹ and others, appears to be more effective in the treatment of diabetes mellitus than painstaking attention to the percentage composition of the diet.

TABLE IV
A Day's Ration by which Approximate Accuracy Is Reached without the Use of the Scales

	CARB	PROT	FAT	CAL
BREAKFAST				
Fruit (one of the following)				
½ small grapefruit, 1 medium peach,				
1 small or ½ medium orange, ½ cup berries,				
½ small or ¼ large cantaloupe	10	1	0	44
Egg one	0	6	6	78
Bacon 4 half or 2 whole slices	0	5	14	146
Cereal or Bread (one of the following)				
Oatmeal, cooked thin, ½ cup,				
Oatmeal, cooked thick, ¼ cup,				
½ cup cornflakes, puffed rice or wheat,				
½ shredded wheat,				
1 small slice of bread, 4x3x½ inches,				
2 soda crackers	10	2	0	48
Cream 2 tablespoons heavy or ¼ cup light	2	2	12	124
Butter 1 tablespoon	0	0	12	108
Coffee or Tea, unsweetened or with saccharine				
Total	22	16	44	548
DINNER				
Broth, clear, fat removed	0	3	1	21
Meat lean, or fish, cooked, 1 slice, 4x3x½ inches	0	16	10	154
Vegetables 5%, no limit,	4	2	0	24
10%, ½ cup cooked	5	1	0	24
Butter 1 tablespoon	0	0	12	108
Cream 1 tablespoon heavy, or 2 tablespoons light	1	1	6	62
Tea or Coffee as for breakfast, if desired	0	0	0	0
Dessert fruit as for breakfast	10	1	0	44
Total	20	24	29	437
SUPPER OR LUNCHEON				
Broth as for dinner	0	3	1	21
Vegetables 5%, no limit,	7	2	0	36
10%, ¼ cup				
Egg one	0	6	6	78
Olive Oil 1 tablespoon, with vinegar	0	0	15	135
Bread 1 small slice or 2 crackers, as for breakfast	10	2	0	48
Butter 1 tablespoon	0	0	12	108
Milk 1 glass (8 ounces)	12	8	10	170
Total	29	21	44	596
Total for 24 hours	71	61	117	1581

REFERENCES

- ¹ATWATER, W O, and BRYANT, A P The chemical composition of American food materials, U S Dept of Agricult Bull No 28, 1906
- ²CHATFIELD, C, and McLAUGHLIN, L I Proximate composition of fresh fruits, U S Dept of Agricult Circ No 50 (Dec) 1928
- ³JOSLIN, E P The treatment of diabetes mellitus, third edition, p 737, 1923, Lea, Febiger & Co, Philadelphia and New York
- ⁴CAMPBELL, W R, and PORTER, M T A guide for diabetics, 1926, Williams and Wilkins Co, Baltimore
- ⁵HUDDLERSON, M P Food for the diabetic, 1924, The Macmillan Co, New York
- ⁶SANSUM, W D The treatment of diabetes mellitus with higher carbohydrate diets, 1929, Harper and Bros, New York
- ⁷NEWBURGH, L H, and MARSH, P L The use of a high fat diet in the treatment of diabetes mellitus, Arch Int Med, 1920, xxvi, 647
- ⁸RABINOWITCH, I M Experiences with a high carbohydrate-low calorie diet for the treatment of diabetes mellitus, Canad Med Assoc Jr, 1930, xxiii, 489
- ⁹ALLEN, F M Methods and results of diabetic treatment, New Eng Med Jr, 1930, ccm, 1133

Myxedema

A Case Report*

By HENRY B. GOTTEN, M.D., *Memphis, Tennessee*

CLASSICAL myxedema is seldom seen. The case reported herein is interesting in that it presents practically all the characteristics of an extreme hypothyroidism.

Mrs. W. D. H., aged thirty, came to the clinic on November 17, 1930, complaining of exhaustion, lack of energy, and weakness, and stating that these symptoms had persisted since the birth of her last child, seven years earlier. She had spent a part or all of each day in bed for a number of years. During that time she had gained about thirty pounds in weight. Menstruation was irregular, the periods appeared every six to eight weeks and were very scant. Her eyes often became very puffy, and her feet were sometimes swollen. She suffered a great deal from colds and was always chilled. Her digestion was very poor; she was unable to eat sweet or greasy foods, was frequently troubled with nausea and vomiting, and for a long while had been severely constipated. On one occasion she had had an acute attack of colic.

The patient was five feet, one inch in height and weighed one hundred thirty pounds. Her skin was pasty in color, was cold, dry, puffy, and did not pit on pressure. A moderate anemia was obvious. Blood pressure was 110/70, pulse 70, and temperature 98 degrees. Reflexes were markedly retarded, particularly on relaxation. Psychic response was sluggish. No other physical signs were found.

The laboratory test of the urine was reported negative. The white blood count was normal, but the red blood count was only 3,400,000, and the hemoglobin 52 per cent.

The basal metabolic rate was minus 42. Roentgenograms of the skull were negative.

The heart was typically myxedematous, being grossly enlarged. The right side measured 57 cm. and the left 112 cm.,—a total of 169 cm. (figure 1). Electrocardiographic tracings revealed a right axis deviation with slurring of the Q R S complexes in all three leads. The voltage was low (figure 2).

Four grams of desiccated thyroid were given each day for a period of two months. During that time the patient improved rapidly. The reflexes returned to normal. Her weight decreased to 110 pounds. The hemoglobin increased to 70 per cent, and the red cell count rose to 3,800,000. At the last examination the pulse rate was 100. The metabolic rate was plus 10. The heart had become normal in size, as shown by the roentgenogram: the right side measured 25 cm. and the left 9 cm.,—a total of 115 cm. (figure 4). The electrocardiograph was considered normal. The Q R S complexes were upright in leads I and II and inverted in lead III, which was interpreted as an axis deviation. The T waves were upright in all of the three leads (figure 3).

Several factors in this case are sufficiently interesting to warrant discussion. The dullness and listlessness characteristic of hypothyroidism were present. Although the psychomotor activity was decreased, the senses were

*Received for publication, September 12, 1931.

normally acute and the mentality seemed unimpaired. Retardation of the reflexes, especially of the Achilles reflex, was one of the findings. The secondary anemia was outstanding, practically all symptoms could have been explained on the basis of pernicious anemia. The cardiac enlargement also marked the disease.

The retardation of all reflexes is a pathognomonic finding of myxedema. The condition is particularly evident on relaxation of the Achilles reflex and may be easily recognized without the aid of mechanical devices.

The first published account of this phenomenon was recorded in 1924, by W. C. Chaney.¹ He found that the kymograph demonstrated a slow Achilles reflex as compared to the normal. Since Chaney showed that in

other diseases characterized by a lowered metabolic rate, as pituitary tumor, this reflex is not retarded, it is always advisable to test the Achilles reflex when the patient has a low metabolic rate. In the more severe forms of anemia, this reflex is normal. Myxedema may thus be further distinguished from pernicious anemia.

An erroneous diagnosis of pernicious anemia is often made in myxedema. Each of the three cases reported by MacKenzie had previously been diagnosed pernicious anemia. Error is especially likely if examination of the gastric contents reveals no free hydrochloric acid. Although hydrochloric acid is present in many cases of myxedema, it is not always a finding, therefore one cannot distinguish myxedema and pernicious anemia by its absence.



FIG 1 Heart in case of myxedema before treatment

Each of twenty-three patients reported upon by Stone was anemic to some extent, in a few the hemoglobin was as low as 40 per cent. The gastric secretions of several contained no trace of hydrochloric acid.

The characteristics of pernicious anemia as opposed to those of the anemia of myxedema are (1) the presence of macrocytes and megalocytes, (2) the high color index, (3) the abnormal appearance of the red blood cells, (4) spinal cord changes, (5) a normal metabolic rate, and (6) a history of remissions and exacerbations of symptoms. The age of the patient is

also a consideration. Pernicious anemia seldom develops in persons so young as the patient in this case.

Zondek⁸ first reported cardiac enlargement in myxedema in 1918 in Germany. In this country it was described by Fahr⁵ in 1925. Davis³ recently collected twenty-one cases in the literature, to which he added another of his own. The enlarged heart, therefore, is now recognized as a feature of this disease.

In the myxedematous heart the chambers are equally dilated. Neither the bulging of the conus arteriosus and pulmonary arteries of mitral stenosis,

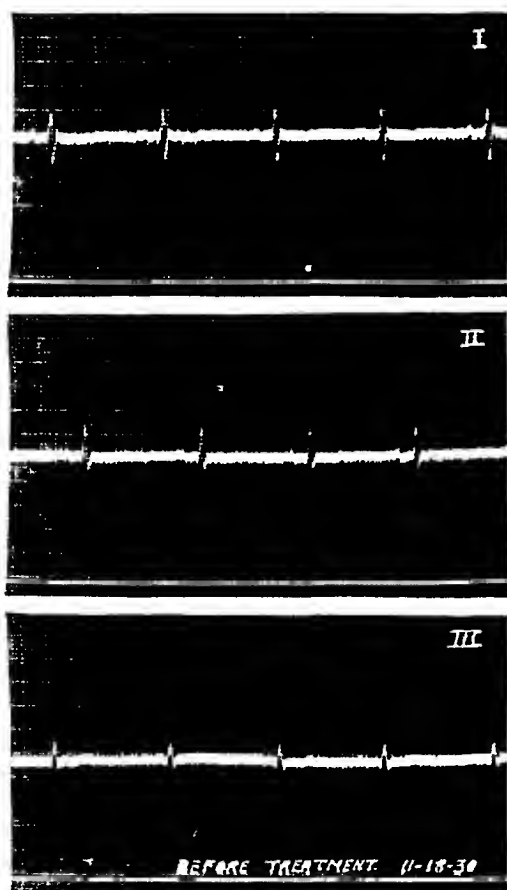


FIG 2 Electrocardiographic tracing in a case of myxedema before treatment. Note low voltage, flat T waves, and increased P-R interval (almost 0.2 sec.)

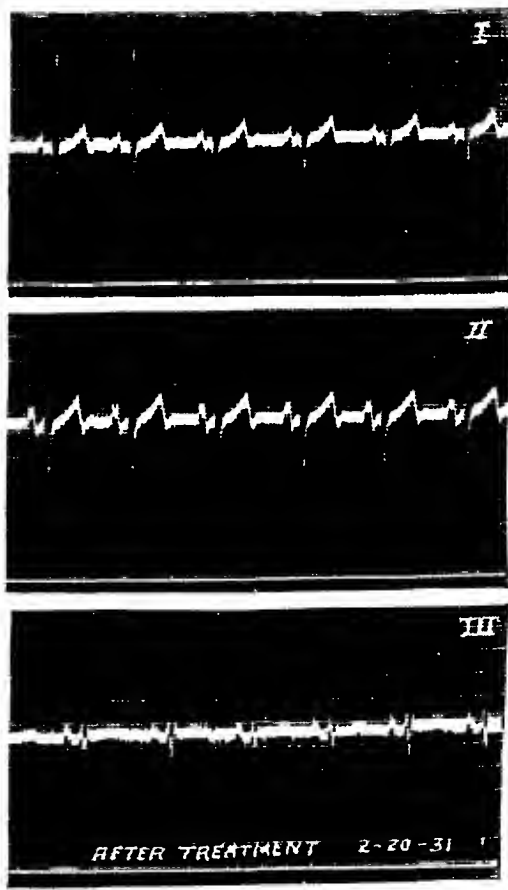


FIG 3 Electrocardiographic tracing in case of myxedema after three months' treatment. Note change in voltage and decrease of P-R interval.

nor the marked dilation of the left ventricle found in aortic lesions or hypertension, is present. The heart under the fluoroscope gives the appearance of a pericardial effusion. It has also been observed that the movements of the cardiac borders are very sluggish, in sharp contrast to the movements of the enlarged heart in other diseases.

The electrocardiographic changes in this condition are characteristic. The P waves may or may not be present, the T waves are usually negative in one or more leads. The P-R interval is abnormal in many cases. The Q R S complexes are notched, frequently inverted, and the time interval is prolonged. If proper treatment is instituted, the heart will be reduced to its natural size. The irregularities of the

electrocardiographic tracing will also disappear. Fahr described several cases in which he withdrew the thyroid substance in order to more conclusively show the effect; the heart again became enlarged and the electrical tracing abnormal. When the thyroxin was resumed, the normal characteristics of the heart returned.

CONCLUSION

Physical and laboratory findings frequently overlooked in myxedema were demonstrated in this case, indicating the necessity for a thorough investigation in order to make a correct diagnosis. The rapid response of the affected systems to appropriate treatment is typical.



FIG 4 Heart in case of myxedema after three months' treatment

REFERENCES

- ¹CHANEY, W C Tendon reflexes in myxedema a valuable aid in diagnosis, Jr Am Med Assoc, 1924, lxxxii, 2013-2016
- ²CHRISTIAN, H A Diagnosis and treatment of heart disease, Oxford Monograph, iii, Oxford University Press, New York, 279
- ³DAVIS, J C Myxedema heart with report of one case, ANN INT MED, 1931, iv, 733-741
- ⁴FAHR, G Myxedema heart, Jr Am Med Assoc, 1925, lxxxiv, 345-349
- ⁵FAHR, G Myxedema heart, Am Heart Jr, 1927, iii, 14-30
- ⁶MACCENZIE, G M Anemia in hypothyroidism, Jr Am Med Assoc, 1926, lxxxvi, 462-464
- ⁷STONE, C T The occurrence of anemia in myxedema, ANN. INT MED, 1928, ii, 215-221
- ⁸ZONDEK, H Das Myxodemherz, Munchen, med Wehnschr, 1918, lxxv, 1180-1182

“We Must Keep the Whole Organism in View”

“**F**INALLY, although I have been seeking a description of certain isolated phenomena occurring during the course of pneumonia, I have not been unmindful of the dictum of Professor Haldane, that in studying biological phenomena “we must keep the whole organism in view”—that the living organism is a whole, not merely a collection of its parts, and that whatever happens in one part of the body affects every other part. Moreover, experience abundantly teaches that conclusions regarding phenomena that occur in the test tube cannot be applied to the living body without reservations, and that what happens in one animal under certain circumstances does not necessarily happen in another under similar conditions. The conditions can never be identical. Biological phenomena can never be fully understood unless in addition to the study of isolated phenomena the “*physis*” also be studied, and by “*physis*” the Greeks meant “the organism—the organism as a whole.” It is this element that medicine must not disregard, but experience teaches that we can best understand the whole by the study of the parts, not as isolated events, but in their relation to the entire organism.”

From *The Nature of Pneumonia*, the Twelfth Pasteur Lecture, by RUFUS COLE M D (Proc Institute of Med, 1932, xi, 2-20)

Hypothyroidism Without Myxedema*†

By JOHN B. YOUNG, M.D., F.A.C.P., and SAMUEL S. RIVEN, M.D.,
Nashville, Tennessee

DURING recent years considerable evidence has accumulated to emphasize the importance of hypothyroidism without myxedema as a separate clinical entity. A growing number of case reports and articles dealing with this condition indicates an increasing appreciation of its frequency and importance. Many of the reports have been from regions where goiter is common but the report of Thompson and Thompson¹ from the New England States, King² from Baltimore, and Higgins³ from Virginia show that the condition is not confined to such areas. The present report from a region where the general incidence of goiter is relatively low gives further evidence of the wide spread distribution of this condition.

However, in spite of this increasing interest, the disease is frequently overlooked because of the absence of signs and symptoms common to the better known form of hypothyroidism, myxedema. Patients with hypothyroidism without myxedema, characteristically present few or none of the better known signs and symptoms of hypofunction of the thyroid. The skin is

usually not dry, harsh, or thick, loss of hair seldom occurs. The patient is not unduly sensitive to cold, and the temperature is not subnormal. The pulse is not slow and may even be more rapid than normal. Hoarseness and mental lethargy, so frequently present in myxedema, are lacking. The disease may occur at any age but many of the patients are young or adolescent. Very often the symptoms are misleading, suggesting disease of other organs and systems and the primary location of the trouble in the thyroid gland is unsuspected. In many instances the accidental discovery of a low basal metabolic rate has been the first clue to the true nature of the trouble.

Nevertheless, these patients do present certain symptoms, or symptom complexes, which should suggest the possible presence of this type of hypothyroidism, particularly if more common causes for these symptoms cannot be found. The most frequent and important of these are constipation, nervousness, poor emotional control, fatigability, lack of energy, and vague pains localized in various regions. The onset of the disease is gradual and insidious and may date back a number of years. Women are more frequently affected than men. The patient never appears acutely ill and the vagueness

*From the Department of Medicine, Vanderbilt University Medical School.

†Received for publication, September 15, 1931.

of the symptoms, together with the absence of significant findings on examination may lead to the diagnosis of a psychoneurosis. The constipation is very intractable and is, perhaps, the most frequent symptom encountered. Nervousness, irritability and lack of emotional control are frequently presenting symptoms. Associated with this nervousness there is a certain lack of energy and endurance, mental as well as physical. This is particularly noticeable in the exhaustion which may follow the performance of the daily duties. Warfield⁴ has described well the active individuals whose energy is forced, and whose activity is followed by an abnormal weariness. To these symptoms may be added loss of weight, a change which is the opposite of that expected in hypothyroidism. This loss of weight, together with nervousness and a not infrequent increase in the pulse rate, may lead to the suspicion of thyrotoxicosis, which is rather startlingly contradicted by the finding of an abnormally low metabolic rate.

Laboratory examinations yield little of significance except the evidence of an abnormally low basal metabolic rate, which ranges from about the lower limit of normal to as low as minus 30 per cent or lower. This, although not pathognomonic of this condition, is the most characteristic finding and is necessary for the diagnosis. Of almost equal importance is the response to treatment with thyroid substance. The significance of these two factors is discussed more fully below. Warfield and Greene,⁵ and others, have described a secondary anemia of the chlorotic type, frequently associated with this type of hypothyroidism. While a secondary

anemia is common in this condition, it is not always present nor is it, of course, sufficiently characteristic to be of particular diagnostic significance.

Considerable confusion exists in regard to the finding of lowered metabolic rates in association with the menopause and other conditions. While it is undoubtedly true that lowered metabolic rates may be the result of other causes than primary hypothyroidism it is likewise true that the latter may occur with other diseases as an associated, not independent, condition.

A correct diagnosis of hypothyroidism is important because of the relief of symptoms which follows specific treatment with thyroid substance, a relief which is so definite that, as will be shown below, it is an important factor in determining the correctness of the diagnosis. It is also important that the diagnosis be made as early in the disease as possible in order that early treatment may prevent the development of structural changes in various organs and tissues, from long continued hypofunction of the thyroid. The effect of such hypofunction of the thyroid on the gastrointestinal tract has been emphasized by Brown.⁶ Barrett⁷ has called attention to the effect on the nervous system. Williamson and Pearse⁸ believed that the functional strain incident to long continued hypofunction is important in causing structural changes in the thyroid gland itself.

The following case reports are presented to illustrate various types of cases and different features of the disease. They have been selected from a total of seventeen cases of this condition observed in this clinic during the

past three years, most of which have been followed for a period of two years or more. In addition to the case reports the significance of certain laboratory findings, the effect of treatment and the relation of this disease to other forms of hypothyroidism are discussed.

REPORT OF CASES

Case I V G, aged 25, a single, white woman was admitted to the medical outpatient department complaining of headaches, nervousness, and pain in the arms. The present illness had begun about seven months before when she first noted a dull aching pain over her head and left side of the face gradually increasing in severity. Increasing restlessness and insomnia were noted. For a year she had been unable to follow her usual occupation of teaching. There was a history of vague gastrointestinal symptoms associated with constipation for several years. The average weight was 132 pounds, and her weight was 128 pounds at the time of her first examination. There was no history of any menstrual disturbance.

Examination revealed a well-developed, well-nourished white female who was cooperative and mentally alert. There was some tenderness over the scalp but none over the sinuses. The pupillary reactions were normal. There was a slight external strabismus of the left eye. The sclera were clear, and the examination of the fundi was negative. The tonsils were small, smooth, not infected. There was a severe gingivitis about many of the upper teeth and diffuse dental caries. The thyroid was not enlarged. Examination of the chest and abdomen gave normal findings. The blood pressure was 126 systolic and 84 diastolic. The skin was soft, warm, dry, clear and of good tone. The neurological examination was negative. All the usual laboratory tests, including the urinalysis, the blood count and the Wassermann reaction, were negative. A tentative diagnosis of psychoneurosis was made, and she was treated with a mild sedative, but did not improve.

On March 16, 1929, she returned to the clinic with the same symptoms as those described a year before. This time a basal

metabolism determination was made, and to the surprise of the observer, the rate was found to be minus 26 per cent. Four days later it was minus 25 per cent. At this time it was thought there was perhaps a slight dryness of the skin, and a thinning of the outer half of the eyebrows. The patient appeared somewhat apathetic and complained of mental sluggishness. There was no edema, and no alteration in weight. A diagnosis of hypothyroidism was made.

Course She was first given thyroid extract 0.13 gms (gr two) daily. On March 30, 1929, the basal metabolic rate was minus 19 per cent. The thyroid extract was increased to 0.065 gms (gr one) three times a day. On April 6, the basal metabolism was minus 10 per cent. The patient said she felt very much improved. Her bowels moved regularly and there was a general feeling of well-being. The thyroid extract was discontinued. On April 16, 1930, she returned with the symptoms of indigestion, fatigability and mental sluggishness. The basal metabolism determination was minus 29 per cent. She was again given thyroid, 0.065 gms (gr one), three times a day. On the 27th of April, she said she felt better, the bowels were regular, the appetite was good and the basal metabolism was minus 21 per cent. The same dose of thyroid extract was continued and on May 25, the basal metabolism was minus 8 per cent. On June 17, she still felt better as compared to first visit, but not as well as at the last visit. The basal metabolism was minus 18 per cent. On August 21, 1929, the patient was seen again with a return of all of her symptoms. She had discontinued thyroid medication and was back where she had started, with a basal metabolic rate of minus 29 per cent.

Comment There is presented a young woman with a metabolism rate within the "myxedema range", who nevertheless showed no myxedema, no change in weight, no menstrual disturbances, and only slight dryness of the skin. Many of the common symptoms of myxedema were lacking. She responded favorably to the administra-

tion of thyroid extract but never had enough to bring the basal metabolism up to normal. Discontinuance of the drug was associated with a return of the clinical features of the disease. Except for the finding of a low metabolic rate and the response to specific therapy there was little to indicate the existence of the hypothyroidism.

Case II B T, white female, aged 48, was seen in the medical outpatient department July 7, 1929, complaining of nervousness, insomnia, increasing irritability and moroseness. In addition she had severe headaches in the back of her head. The menopause had begun some two years before and the uterus had been removed a year before admission. Examination revealed a well-developed, and well-nourished woman. The examination of the ears, eyes, nose, and throat was negative. The thyroid isthmus was distinctly enlarged, but the lobes were barely palpable. The remainder of the examination was normal. The blood pressure was 140 systolic and 80 diastolic. The weight was 115 pounds. The skin was fine in texture, elastic, of good quality, and normally warm and moist. A tentative diagnosis of psychoneurosis was made but the basal metabolism was found to be minus 17 per cent. A second test the following day was again minus 17 per cent. The patient was given thyroid extract, 0.1 gm (gr one and one-half), daily, and in three weeks the basal metabolic rate had risen to plus 5 per cent. The thyroid extract was discontinued for ten days and the basal metabolism promptly dropped to minus 26 per cent. Thyroid extract was then given in doses of 0.065 gms (gr one) three times a day for three days and 0.065 gms (gr one) twice daily for three days and then 0.1 gms (gr one and one-half) daily. On September 19, the patient returned feeling quite well. The basal metabolic determination was minus 7 per cent. Thyroid extract 0.1 gms (gr one and one-half) daily was continued during a period of fifteen months, the basal metabolism ranging between minus 8 and plus 1 per cent. On October 3, 1930, she came for a chat say-

ing she was very much improved and had continued to take thyroid extract, 0.1 gms (gr one and one-half), daily.

Comment This case is an example of a lowered metabolic rate following the menopause. Because of the favorable response to treatment with thyroid extract, both subjectively and in the effect on the metabolic rate, a diagnosis of hypothyroidism independent of the menopause is warranted.

Case III Z M, a married woman, aged 42, was admitted to the medical outpatient department on August 2, 1929, complaining of nervousness, and mental depression. All her life she had been more or less nervous as were many members of her family. Ten months before her admission, her menstruation had ceased and two months later she had had influenza. Following the attack of influenza she felt weak, much depressed, emotionally unstable, and was forced to stay in bed for two months. One month before her admission, she had had a severe menstrual period lasting four days. Following this the nervousness increased, her appetite was poor and she lost weight. There had been no noticeable skin changes, and no constipation. The physical examination was essentially negative save for emaciation, she weighed only eighty-nine pounds. The urinalysis and Wassermann tests were negative. The blood showed a moderate secondary anemia with a hemoglobin of seventy per cent. A tentative diagnosis of psychoneurosis and undernutrition was made. The patient was treated with sedatives and psychotherapy but made no progress. On October 12, the basal metabolism was found to be minus 11 per cent. She was given thyroid extract, 0.38 gms (gr one-half), twice a day and improved somewhat. On December 2, the basal metabolic rate was still minus 11 per cent and the thyroid extract was discontinued. Within one week the rate dropped to minus 20 per cent. Thyroid extract was again given in doses of 0.38 gms (gr one-half) three times a day, but this amount produced no change in the basal metabolic rate and few changes in the symp-

toms On January 27, 1930, the basal metabolic rate was minus 22 per cent It was decided to push the drug and she was given 0.13 gms (gr two) daily The basal metabolism rose to minus 10 per cent, the patient felt very much improved, began to gain weight and the nervousness disappeared By April 10, 1930, she had gained eight pounds, the metabolic rate was minus 1 per cent and the thyroid extract was continued On June 10, the basal metabolism was minus 6 per cent, her weight was 102 pounds and she felt well The thyroid extract was reduced to 0.065 gm (gr one) and 0.13 gm (gr two) on alternate days She was observed from August to October during which time she continued to improve, the basal metabolism ranging from minus 6 to plus 6 per cent During that interval she gained 6½ pounds

Comment This patient was very much improved with thyroid extract, and such features as loss of weight, nervousness, and mental sluggishness disappeared Symptoms referable to the menopause were little affected It is interesting to note that an initial low metabolism became even lower after thyroid medication, once started, was discontinued, and that rather large amounts of the thyroid extract were necessary to raise the metabolism to a normal level The significance of these observations is more fully discussed below The administration of amounts sufficient to raise the metabolism to normal was necessary to secure subjective improvement

Case IV J T, woman, aged 20, was admitted to the medical outpatient department on September 3, 1929, complaining of nervousness and abdominal distress An appendectomy had been performed for these symptoms with no relief Her appetite was variable and for a long time she had suffered with constipation She was troubled with disturbed sleep and worried a great deal

The examination revealed a well-developed,

well-nourished young woman of normal weight (112 pounds), who was very emotional and apprehensive The skin was coarse and dull, the mucous membranes were pale The eyes, ears, nose, and throat were essentially normal The thyroid was slightly enlarged at the isthmus, otherwise normal The examination of the heart and lungs was normal The blood pressure was 105 systolic and 45 diastolic There was a scar in the right lower quadrant of the abdomen, but no tenderness, no spasm, no masses and no palpable organs

The tentative diagnosis was a functional disturbance of the gastrointestinal tract, constipation and mild secondary anemia Treatment was directed toward these, but with no improvement On her third visit to the clinic a basal metabolism determination was obtained and the rate was minus 17 per cent A check determination on October 5, was minus 23 per cent She was then given thyroid extract 0.65 gms (gr one) three times a day After one week the rate rose to minus 3 per cent The patient was advised to continue with thyroid extract, 0.13 gms (gr two) daily and a week later the metabolism dropped to minus 10 per cent The dose of thyroid was increased to 0.2 gms (gr three) daily, and the metabolic readings varied from minus 17 per cent to plus 3 per cent, depending on how conscientious she was about taking her medication Finally her symptoms were controlled with 0.13 gms (gr two) of thyroid extract daily The course of observation lasted over a period of eight months and space does not permit enumeration of the numerous metabolism readings It must however, be mentioned that there were times, when the metabolism approached normal that the patient had nervousness and mild tremor The best symptomatic improvement was observed with the basal metabolism at a level of minus 3 per cent During the period she was receiving thyroid extract she gained weight and the emotional instability and constipation were controlled

Comment A young woman with none of the usual findings in the history and examination suggestive of myxedema was found to have a dis-

tinctly lowered metabolic rate and showed a decided improvement when given thyroid extract

Case V A H., a white woman, aged 33, was admitted to medical outpatient department on September 13, 1929, complaining of a dull pain around the heart which had been present for 18 months and was not particularly related to exertion or excitement. There was no history of rheumatic fever. At times she felt weak, apathetic and fatigued, at others was very nervous and "jumpy". There had been a slight loss of weight (6 pounds). She had had frequent headaches in the past. There was no constipation. The menstrual history was normal.

Examination revealed an alert, healthy appearing young woman. Her skin was clear, smooth, and not cold. The examination of the heart and lungs was normal. The blood pressure was 105 systolic and 65 diastolic. Abdominal and pelvic examinations were negative. The Wassermann test and urinalysis were negative. The electrocardiogram was normal. The blood showed a slight secondary anemia, with the hemoglobin 66 per cent and the red blood cells 3,480,000. A tentative diagnosis of effort syndrome was made. On September 29, the basal metabolism was minus 28 per cent. She did not return to the clinic again until March 18, 1930, when the basal metabolic rate was found to be minus 24 per cent. The symptoms were the same.

Although this patient was not treated with thyroid extract the abstract is presented because there is illustrated an individual in the fourth decade of life, with no menstrual disturbances, no skin changes, without sensitiveness to cold, with certain symptoms such as emotional instability, fatigability and vague pains which are commonly seen in this type of hypothyroidism and an initial metabolic rate of minus 28 per cent. After a period of seven months without treatment, the same symptoms of hypothyroidism remain, the metabolism

is minus 28 per cent and there is no myxedema.

DISCUSSION

The existence of a syndrome such as that described above has naturally aroused discussion as to the exact relation between this and other forms of hypothyroidism and numerous classifications of the latter have been suggested. The most recent is that of Warfield,⁴ who divides hypothyroidism into three main groups: cretinism, myxedema of adults, and masked or occult hypothyroidism, the latter the condition which has been described here. Whether or not this hypothyroidism is to be considered a forerunner of myxedema or a premyxedematous stage of myxedema is questionable. Several of our patients have been observed over a period of months without the development of myxedema even though untreated. If one may judge from the history, the condition in some patients may have been present for years without the development of myxedema. Such evidence is not entirely convincing, however, since myxedema may be very gradual and insidious in its onset. Other evidence, however, supports the view that this type of hypothyroidism exists as an independent syndrome. The existence of a metabolic rate as low as minus 30 per cent for considerable periods of time without the appearance of myxedema is very suggestive. The occurrence of a definitely lowered metabolism in such conditions as inanition and the like without the presence of myxedema, with associated structural changes in the gland, is also important. Of particular interest in this connection is the work of Williamson and

Peaise⁸ who have described a specific pathologic change in the gland in myxedema, and who distinguish on the basis of these pathological studies between myxedema and other forms of hypothyroidism

Some question may be raised as to the justification of the diagnosis of hypothyroidism when the above symptoms and a lowered metabolic rate are found in association with such conditions as the menopause or various other disease states. Since the symptoms are not particularly characteristic it becomes largely a matter of interpretation of the lowered metabolic rate, the significance of which is more fully discussed below. Thurmon and Thompson⁹ have recently stated that in many of these cases there is no primary hypothyroidism. We agree that this is true in many instances and the correctness of this view is supported by the failure in many cases, of thyroid substance to relieve the symptoms even though the basal metabolism is brought by this means to normal levels. We believe, however, that in certain cases, an independent hypothyroidism may exist in association with such conditions as the menopause and in these cases, existence of a primary thyroid disease as a cause of at least part of the syndrome is borne out by the improvement in certain of the symptoms by the administration of thyroid extract. Case two is an example of such an instance.

It is apparent that in the absence of characteristic symptoms and physical signs, great dependence is placed on the finding of a low basal metabolic rate. It is important, therefore, that the significance of this laboratory finding be clearly understood. Low basal meta-

bolic rates do not always mean hypothyroidism. They may be observed in trained subjects (because the usual clinical standards are too high for this group), in inanition, and with loss of muscular tone, as well as with disturbances of other glands of internal secretion. Thurmon and Thompson⁹ have recently classified patients with low basal metabolic rates into three groups, as follows: (1) those who are apparently healthy and have a low metabolism, (2) those with hypothyroidism too mild to result in myxedema, and (3) those in whom a lowered metabolism is associated with a pathological condition other than underfunction of the thyroid. We are in accord with this classification but emphasize that low rates mean hypothyroidism if the first and third group are ruled out, and further, that the determination of the basal metabolic rate is not only of great importance but a necessary means of making such a diagnosis. The common errors in the determination of the basal metabolic rate give falsely high values rather than low, and with rare exceptions falsely low rates cannot be obtained. Boothby and Sandiford,¹⁰ in a series of what they call questionable hypothyroidism, found in eighty-six cases an average below minus 20 in thirty, and below minus 11 in sixty-one instances. Means and Burgess¹¹ state that a low basal metabolic rate means hypothyroidism provided hypopituitarism, Addison's disease, starvation, et cetera, are ruled out. Therefore, in the absence of such conditions, with basal metabolic rates below minus 20, without frank myxedema, but with the symptoms mentioned above, a diagnosis

of hypothyroidism of the type described in this paper must be considered. The main difficulty of interpretation occurs in the case of individuals with a rate between minus 10 per cent and minus 20 per cent. In such instances we feel that in the presence of symptoms such as fatigability, mental sluggishness and constipation, a metabolism of minus 10 per cent or less strongly suggests hypothyroidism provided that the symptoms are relieved by the administration of thyroxin or thyroid extract coincident with a return of the basal metabolic rates to normal levels. If we interpret it in this way, a low metabolism may be safely used in this diagnosis.

Of particular importance in connection with the finding of basal metabolic rates in the neighborhood of minus 10 per cent are the observations in cases two and three. It will be noted that when treatment with thyroid substance was stopped after a short period of administration, the basal metabolic rate which had been minus 17 per cent in case two, and minus 11 per cent in case three, fell within a short period to a much lower level. The following explanation for this finding is suggested. There is evidence for the belief that the administration of thyroid substance to a normal subject leads to a certain amount of decreased function and atrophy of the gland. In the cases described it may be that the thyroid gland, though functionally insufficient, was able by straining to maintain the metabolism at a near normal level. Relieved of the stimulus to this activity by an artificial supply of hormone its activity fell to a subnormal level as shown by the

lower metabolic rate, when the administration of thyroid stopped. If this explanation is correct it is possible that such a procedure would be of diagnostic importance in border line or mild cases of this condition.

The nature of the response to the administration of thyroid substance or thyroxin is of great importance. As a means of establishing the diagnosis it is of even greater importance than the determination of the basal metabolism since it serves to distinguish between the lowered metabolic rates due to primary and secondary hypothyroidism. In many cases the nature of the response to the drug may be the final evidence which establishes the diagnosis. In true primary hypothyroidism the relief of symptoms is strikingly quick and complete if a proper amount of the drug is used. A return of the symptoms characteristically follows a withdrawal of the drug. The patients are able to tolerate much larger doses without the development of symptoms of hyperthyroidism than are normal subjects. In many cases the amounts of thyroid necessary to raise the metabolic rate to normal and relieve the symptoms is larger than is generally appreciated. This amount will vary in individual patients, as will the level of metabolism at which maximum relief of symptoms is obtained and both must be determined by trial for each individual. The amounts which may be necessary and which may be well tolerated are shown in the case reports presented above. Symptoms of hyperthyroidism of course occur with too large amounts and over dosage should be avoided.

In contrast to true hypothyroidism,

thyroid substance is ineffective in cases of lowered basal metabolic rate due to other causes and may even make the symptoms worse. However, in those instances in which a true hypothyroidism exists in association with other conditions, such as the menopause, the administration of thyroid substance may relieve the part of the symptoms due to the hypothyroidism, as in case two. Such a result may be considered as evidence of the existence of more than a single disease.

SUMMARY

Hypothyroidism without myxedema is a more common condition than is generally appreciated and is not confined to regions where goiter is com-

mon. Failure to recognize the disease is due to the vague symptomatology and to the fact that the signs and symptoms of the better known hypothyroid state, myxedema, are lacking. The diagnosis depends largely on the detection of an abnormally low basal metabolic rate, but this observation must be interpreted with caution since all low rates are not due to hypothyroidism. In diagnosis, the nature of the response to thyroid substance, which is specific in true hypothyroidism, is of great importance and serves to distinguish between lowered metabolic rates due to hypothyroidism and those due to other causes. Illustrative case reports are presented.

REFERENCES

- ¹THOMPSON, W. O. and THOMPSON, P. K. Low basal metabolism following thyrotoxicosis, permanent type without myxedema, *Jr Clin Invest*, 1928, v, 471-501.
- ²KING, J. T., JR. Hypothyroidism, *So Med Jr*, 1924, xlvii, 662-669.
- ³HIGGINS, W. H. Incipient hypothyroidism, clinical study, *Jr Am Med Assoc*, 1925, lxxv, 1015-1017.
- ⁴WARFIELD, L. M. Hypothyroidism, *Jr Am Med Assoc*, 1930, xcv, 1076-1080.
- ⁵WARFIELD, L. M., and GREENE, I. W. Hypothyroidism and its relationship to chlorotic anemia, *Jr Mich State Med Soc*, 1925, xxiv, 79-82.
- ⁶BROWN, T. R. Hypothyroidism as a cause of intractable constipation, *Trans Assoc Am Phys*, 1926, xli, 162-167.
- ⁷BARRFET, A. M. Hereditary occurrence of hypothyroidism with dystrophies of the nails and hair, *Arch Neur, and Psychiat*, 1919, ii, 628-637.
- ⁸WILLIAMSON, G. C., and PEARSE, I. H. The pathological classification of goiter, *Jr Path and Bact*, 1925, xxviii, 361-387.
- ⁹THURMON, F. M., and THOMPSON, W. O. Low basal metabolism without myxedema, *Arch Int Med*, 1930, xli, 879-897.
- ¹⁰BOOTHBY, W. M., and SANDIFORD, I. Summary of the basal metabolism data on 8,614 subjects with especial reference to the normal standards for the estimation of the basal metabolic rate, *Jr Biol Chem*, 1922, liv, 783-803.
- ¹¹MEANS, J. H., and BURGESS, H. W. The basal metabolism in non-toxic goiter and in borderline thyroid cases, *Arch Int Med*, 1922, xxx, 507-516.

Ventricular Paroxysmal Tachycardia With Report of a Case*†

By EDWARD W. HOLLINGSWORTH, M.D., F.A.C.P., *Veterans
Administration, Hines, Illinois*

PAROXYSMAL tachycardia may be defined as an abnormally rapid heart action with sudden onset and offset, and is divided according to the site of origin of the impulse which may be in the auricle, auriculo-ventricular node, or ventricle.

In general, the important point is to differentiate those examples of ventricular origin from others inasmuch as in them the prognosis is grave. There are several points of distinction clinically between auricular or supra-ventricular, and ventricular paroxysms, the former having a practically constant rate in the various attacks and being frequently stopped by vagal pressure,¹ especially left, the latter varying in rate between various attacks and even during the same attack,² and not controlled by vagus pressure.³ A few cases of ventricular paroxysmal tachycardia have been reported as due to digitalis⁴ (where the usual dosage was not exceeded), and quinidine,⁵ but in the absence of medication are usual-

ly due to serious myocardial disease, most commonly myocardial infarction,⁶ and have frequently been produced experimentally in animals by coronary ligation.⁷

Paroxysmal auricular flutter and fibrillation are not included and can usually be detected by clinical means, the latter by its irregularity increased upon exercise, the former by sudden halving or doubling of the previous rate, which if irregular, is usually less so upon exercise.

The one positive method of identification of ventricular tachycardias is the electrocardiogram,⁶ which, however, frequently offers difficulties. If the tracings show rapid rate with abnormal QRS complexes and P waves at a different rate, or absent, or if they show onset or offset, the diagnosis may be established. As a matter of fact it is believed that P waves may not be seen or their relationship established and the showing of the onset or offset of a paroxysm would usually be purely accidental. Premature contractions may be frequent between attacks and should show complexes similar to those present during them. A further point of confusion is the frequent abnormality of QRS in tachycardia of other origin.⁸ One reports a case of paroxysmal

*Published with the permission of the Medical Director, Veterans Administration, who assumes no responsibility for the opinions expressed or the conclusions drawn by the writer.

†Received for publication, September 3, 1931.

ventricular tachycardia with some hesitation as the diagnosis in many reported cases has been questioned by later writers. Thus Robinson and Herrmann⁶ accepted only six of sixteen as undoubted cases, Scott⁹ doubted the diagnosis in three of the four cases they reported, and Strauss¹⁰ stated only 63 undoubted cases had been reported to 1930. It is believed that but few, if any, cases have been reported having all the characteristic findings, but the following case apparently has, and is accordingly reported as such.

CASE REPORT

J. M., a white male, age 39, occupation, draftsman, was admitted to the Edward Hines Jr. Hospital, June 22, 1927, with a diagnosis of diabetes mellitus and decompensated heart. His complaints were "weak heart", difficulty in breathing, cough, rapid pulse, edema of practically entire body. Family history was negative. He had had the usual childhood diseases, and pneumonia eight years before. He was married, with wife and three children living and well. Smoked cigars, drank occasionally.

Present Illness. On May 5, 1927, while spading in his garden he had a heart attack, heart fluttered and was very rapid, and he felt weak. A second attack occurred a few minutes later but the patient felt all right after resting. During the night he became short of breath, and this had continued until admission, as had edema which developed shortly after the onset. He had been treated at another hospital for heart disease and diabetes, being on a diet and receiving 15 units of insulin daily.

Physical Examination. The patient was a well nourished and developed white male of 40, orthopneic, edematous and critically ill. There was diminished resonance at the lung bases and coarse râles throughout. The heart was apparently enlarged and the apex beat diffuse and wavy. Radial pulse was weak, regular, rate 150, blood pressure 146/90. There were signs of ascites and the scar of a recent abdominal paracentesis.

Laboratory Findings. Urinalyses showed a

very faint trace of albumin, occasionally a faint trace of sugar, specific gravity 1.010, occasional hyaline and granular casts and red blood cells. Twenty-four hour output varied from 600 to 3,500 cc. Glucose tolerance test showed a delayed utilization, blood chemistry was normal, Wassermann test was negative. Roentgenogram of chest showed an enlarged heart with area of infiltration at the lung bases.

Course. There was slight fever from June 27 to July 3. The temperature varied from 36° to 38° C., pulse from 80 to 155, usually about 100. Pulse was noted as weak, sounds distant and feeble, on several occasions, and pulse was intermittent and irregular at times. Patient was put at rest, fluids restricted, and he was given digitalis and theobromine-sodio-salicylate. The edema practically cleared up and he was discharged August 2, considerably improved.

He was readmitted nine days later, on August 11, with edema again present, blood pressure then being 96/66. Diuretic regime was again instituted with ammonium salts and novasurol, and several doses of tryparsamide were given because of a history suggestive of syphilis and a 4 plus Kahn test. Two blood counts showed

4,460,000 red blood cells, 60% hemoglobin, 16,000 white cells, 60% polymorphonuclears, 4,360,000 red blood cells, 60% hemoglobin, 14,200 white cells, 75% polymorphonuclears. Mouth temperature showed a number of slight elevations, 37.2° to 37.4°, pulse varied from 60 to 120 with an average of 84. The edema cleared up and the patient was discharged on December 13.

He then worked steadily at a clerical position for about six months and was admitted for a third time, June 11, 1929, having been very weak, with pulse rapid, for the previous week. At that time the apex impulse could not be seen or felt, radial pulse was weak and irregular, apex rate 198 and apparently regular. The heart sounds were of fair quality and there was no edema. X-ray suggested pericardial effusion and showed a large pleural adhesion attached to the dome of the left diaphragm at junction of outer and middle thirds.

The patient was put on large doses of digitalis and on June 14 the rate was 186,

June 16, 160, and June 18, 80 There had been slight cough and the patient slept poorly but there was no edema, only moderate dyspnea and heart was not noticeably dilated At that time it was felt that the form of the complexes on the electrocardiogram, the variation in rate, the long duration of the paroxysm, and the severity of the heart lesion, suggested a ventricular tachycardia, and that the sudden onset during exercise in a man of sedentary habits, short and inclined to obesity, with no history of previous heart disease, suggested a coronary lesion despite almost complete absence of pain

Treatment was the same as before There were a number of paroxysms of tachycardia, the terminal attack commencing on January 29 and continuing, with but a few hours interval, until death on February 11 There was edema of the lower extremities and heart sounds were tick-tack in character On February 3 the bladder became distended,

the patient was unable to void and 1,000 c c of urine were obtained by catheterization Congestive failure gradually increased, dyspnea being only moderate and the patient conscious almost until the end

POSTMORTEM EXAMINATION

The heart was large, weighing 400 grams, dilated, particularly on the right side, there were pericardial adhesions anteriorly and considerable subepicardial fat, posterior wall of left ventricle was 15 mms thick, anteriorly the wall from the aortic ring to the apex consisted almost entirely of scar tissue, 4 mms thick, and exceedingly resistant There was a mural thrombus in the lower part, 6 by 5 cms, 14 mms thick at the apex, lamellated in the middle portion and light gray in color, and an infarct was seen some $4\frac{1}{2}$ cms in diameter over the corresponding area externally (Figure 1) There was no bulging of the scar There was no evidence

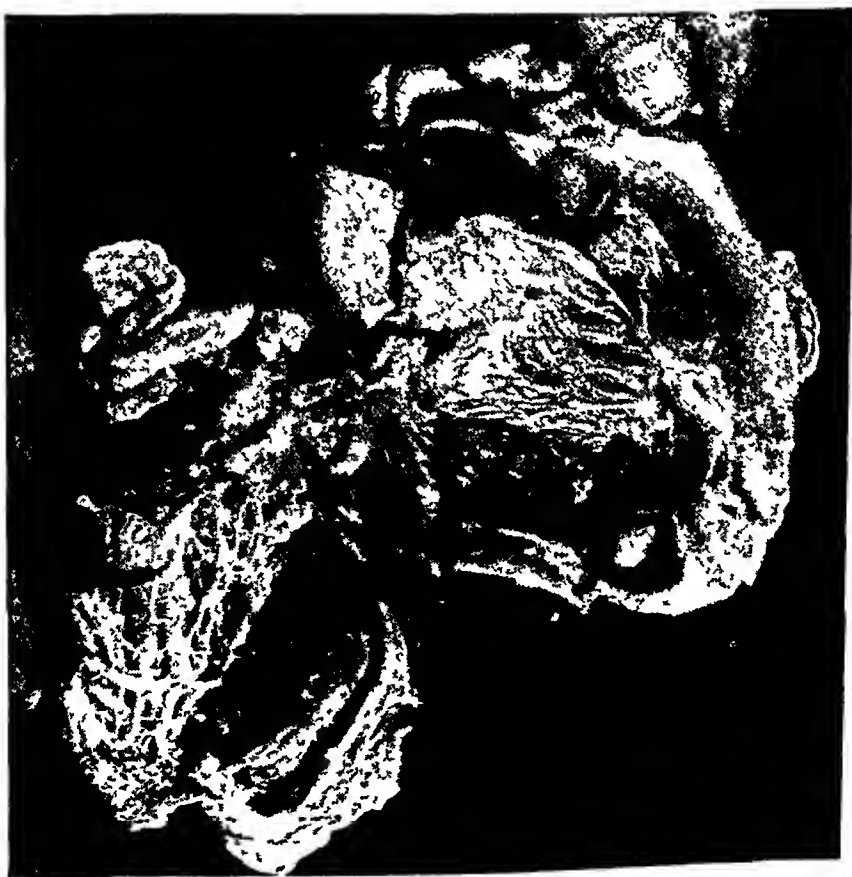


FIG 1 Left ventricle opened through posterior wall, showing scar tissue and thrombus in anterior wall

of syphilis, the aortic ring showed only moderate atheroma, and coronary orifices, auricles and right ventricle appeared normal. The left descending coronary artery was followed downward for 75 cms where it entered the infarcted area and was lost. Both this and the circumflex branch were thickened, with lining rough and irregular. The right coronary showed moderate sclerosis but its lumen could be traced to the septum. The anterior $2\frac{1}{2}$ cms of the left ventricular surface of the septum showed scar tissue.

The left half of the diaphragm showed dense adhesions to the chest wall. The liver weighed 2,250 gms and was typically nutmeg. The spleen weighed 170 gms with poorly defined markings. There was much fat in the omentum and mesentery. There were 300 cc of serous fluid in the right chest.

Microscopic Examination Section through upper part of the anterior wall of the left ventricle showed muscle fibers pale, and cross striations hazy, in places replaced by fibrous tissue. There was a round cell infiltration, the cells for the most part being lymphoid with a few large mononuclears. The small vessels present showed slight intimal thickening. The larger coronaries were not included in the section. Section through the infarcted area showed practically no identifiable muscle fibers, there being almost complete replacement by fibrous tissue. New capillaries were present. There was much round cell and mononuclear infiltration and one area of anemic necrosis completely surrounded by fibrous strands. Kidneys showed a severe nephrosis, lungs, a bronchial pneumonia, liver, spleen and lungs, chronic passive congestion.

Paroxysms of Tachycardia In all seventeen paroxysms were noted, the shortest recorded duration being twenty minutes, and the longest, the terminal attack, was unusually long,⁸⁻¹¹ thirteen days. There was one of four and one of five days, and two of seven days. Abdominal, ocular and vagus pressure were ineffective. Levine³ has noted variation in the apical first sound

and irregularity in rate, the latter only being noted in this case, there being considerable variation of rate in different paroxysms and even in one which lasted for a considerable length of time.

A number of electrocardiograms were taken. The first (figure 2) was taken during the second admission, on August 24, 1927, and showed a rate of 214 with abnormal QRS, these being inverted in I and II, and T waves opposite in direction. P waves were distinct in III only, a P coming at the same rate as the QRS, immediately after the preceding QRS and 0.2 sec before the succeeding one. In this case neither onset nor offset was shown so that according to Lewis⁸ the origin cannot be determined definitely and the QRS aberration may well be due to rapid rate, al-

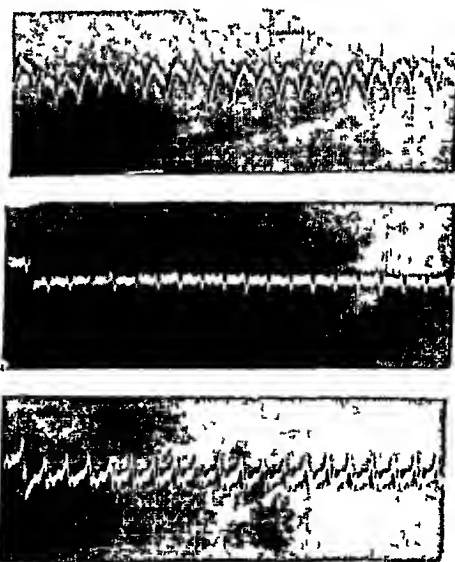


FIG 2 Electrocardiogram taken August 24, 1927. Ventricular rate 214, showing well marked and abnormal P waves in lead III only, at the same rate as the QRS. Paroxysmal tachycardia of an indefinite origin although abnormal QRS and their similarity to some in figure 5 suggest a ventricular one.

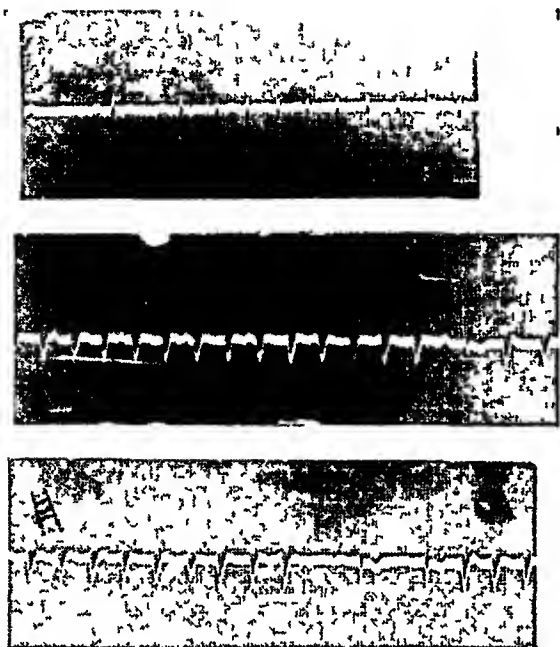


FIG 3 Electrocardiogram taken June 17, 1928, showing a ventricular tachycardia. QRS complexes are aberrant, P waves may be distinguished in all leads at a rate unrelated to the ventricular, and all leads show normal complexes followed by periods of tachycardia, the first beat bearing the relation of a ventricular premature contraction to the preceding normal rhythm

though similar ones are shown in a later tracing (figure 5). The tracing is very similar to one of Robinson and Herrmann's⁶ where P was distinct only in II and at half the ventricular rate. Figure 3 shows a paroxysm of tachycardia with aberrant QRS's of different form, rate 171, interrupted in all leads by normal complexes, and the auricular rate 83, P being easily distinguishable in II and bearing no constant relationship to QRS.

Figure 4 shows an electrocardiogram taken on January 24, 1929, and represents a paroxysm with a rate of 200, the QRS complexes resembling those of figure 3, but are very much higher, which is accounted for in part by improper standardization. Each alternate

T wave is high and is believed to represent a fusion of T and retrograde P. Figure 5 shows another tracing taken on September 18, 1928, and apparently represents a ventricular tachycardia with impulses arising irregularly in both ventricles and at various places in each.

A number of tracings were taken during normal rhythm, the first of which (figure 6) shows small QRS complexes, left axis deviation, inversion of T I. Electrocardiogram on June 18, 1928, (figure 7) shows a typical coronary T wave in II and III, the former coming off below the baseline and T I upright. Two days later T II and III were slightly inverted and then gradually disappeared. Both of these latter showed frequent premature contractions of ventricular origin, the QRS resembling those of paroxysms. According to Barnes,¹² these tracings would indicate occlusion of the right

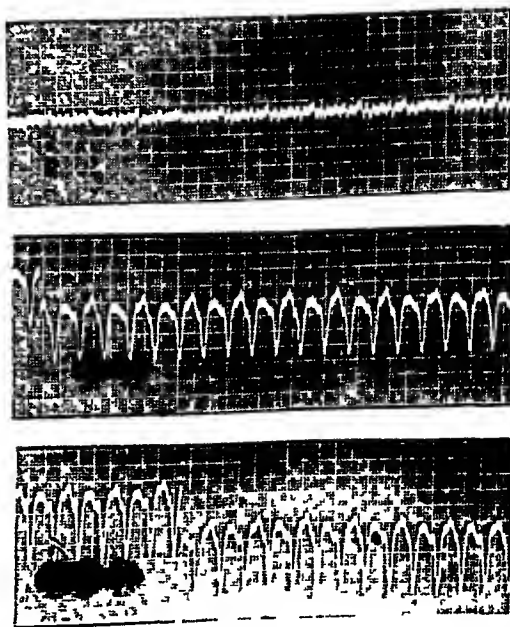


FIG 4 Tracing taken Jan 24, 1929, showing ventricular tachycardia, rate 200, aberrant QRS. In II and III, alternate T waves are high due to super-imposed retrograde P waves

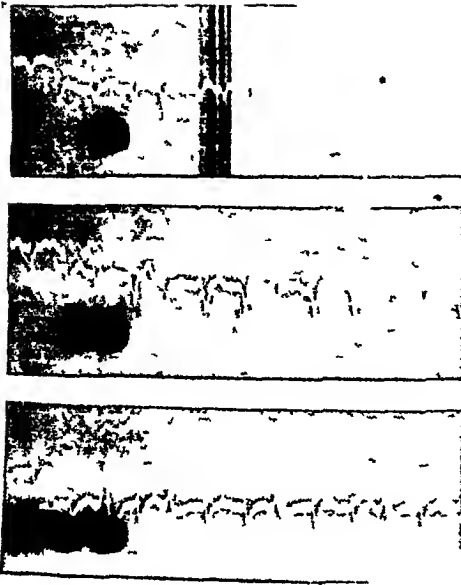


FIG 5 Electrocardiogram taken Sept 18, 1928, showing complexes arising irregularly from various points in both ventricles

coronary artery with infarction in the posterior and basal portions of the left ventricle, but in the present case the left artery was occluded and the anterior wall infarcted

The Relationship of Medication to Tachycardia As either a causative or therapeutic factor, this is a matter of some doubt. Paroxysms occurred while the patient was receiving digitalis in small and moderate doses, quinidine, both digitalis and quinidine, and in absence of medication. One attack stopped on the second day two hours following 0.2 grams of quinidine, a second one after two such doses, and a third attack when several doses of 0.4 grams had been given four hours apart. The terminal paroxysm was apparently uninfluenced by even fairly large doses of quinidine, although these were small compared to those recommended by Levine and Fulton¹³ who restored normal rhythm in eight of ten

cases. They strongly recommended its use, giving as much as 1.5 grams every five hours, and Strauss¹⁰ stated that quinidine was effective in all sixteen cases collected by him in which it was tried. Digitalis seemed to have but little effect upon the heart failure.

The evidences in this case for a ventricular origin of the tachycardia are etiological, coronary occlusion with myocardial infarction, as established by autopsy, repeated attacks of tachycardia with varying rates and abnormal QRS complexes, P waves appearing at different rates, related or unrelated to those of the QRS, premature contractions showing complexes resembling those during tachycardia. The patient's age, 39, and practically complete absence of pain are considered unusual in coronary occlusion, but the customary leukocytosis, fever and low blood pressure were present, no physical signs of pericarditis were obtained, although this was found at

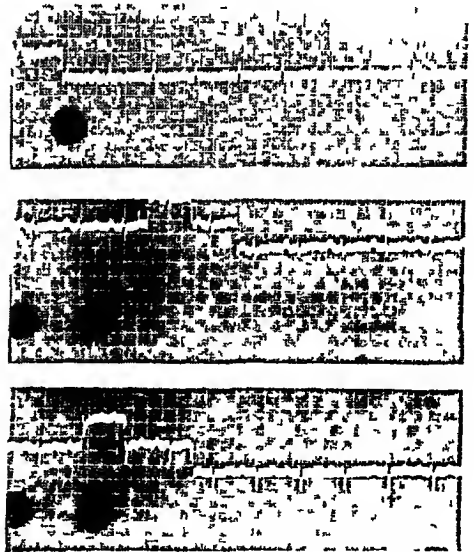


FIG 6 Electrocardiogram of Oct 14, 1927, showing small QRS, left axis deviation, P-R interval of 0.2 sec

autopsy The association with diabetes is not uncommon It seems probable that the patient had his initial occlusion at the time of the onset, although electrocardiographic evidence is lacking, and later, subsequent ones with extension of the infarction Autopsy findings showed that the lesion was of long standing at least

SUMMARY

A case is reported of paroxysmal ventricular tachycardia with numerous attacks, occurring in a white male of 39, with death occurring during tachycardia one year and eight months after onset, the final paroxysm being of thirteen days duration Numerous electrocardiograms were taken and autopsy confirmed the diagnosis of coronary occlusion with myocardial infarction

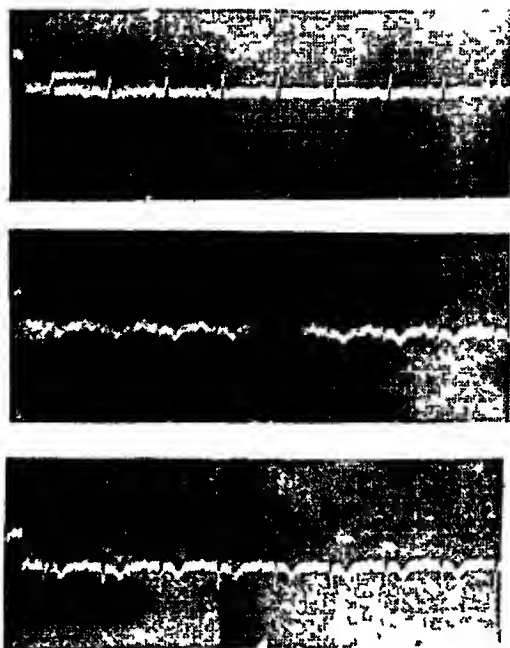


FIG. 7 Electrocardiogram of June 18, 1928, showing inverted coronary T waves in II and III with low take-off in former QRS about same as in figure 6 T I now upright

REFERENCES

- ¹COHN, A E and FRASER, F R Paroxysmal tachycardia and the effect of stimulation of the vagus nerves by pressure, *Heart*, 1913-14, v, 93-108
- ²STRONG, G F, and LEVINE, S A The irregularity of the ventricular rate in paroxysmal ventricular tachycardia, *Heart*, 1923, x, 125-131
- ³LEVINE, S A The clinical recognition of paroxysmal ventricular tachycardia, *Am Heart Jr*, 1927, iii, 177-179
- ⁴SCHWENSEN, C Ventricular tachycardia as the result of the administration of digitalis, *Heart*, 1921-1922, ix, 199-205
- ⁵LEVY, R L Clinical studies of quinidine II Alterations in the cardiac mechanism after administration of quinidine to patients with auricular fibrillation with consideration of certain toxic effects of the drug, *Arch Int Med*, 1922, xxx, 541-477 (Levine¹¹ and Fulton¹³ have criticized the author's interpretation of his curves apparently with justification)
- ⁶ROBINSON, G C, and HERRMANN, G R Paroxysmal tachycardia of ventricular origin and its relation to coronary occlusion, *Heart*, 1921, viii, 59-81
- ⁷LEWIS, T The experimental production of paroxysmal tachycardia and the effects of ligation of the coronary arteries, *Heart*, 1909-1910, i, 98-137
- ⁸LEWIS, T The mechanism and graphic registration of the heart beat, 1925 Shaw & Sons, London, 255
- ⁹SCOTT, R W Observations on a case of ventricular tachycardia, with retrograde conduction, *Heart*, 1922, ix, 297-309
- ¹⁰STRAUSS, M B Paroxysmal ventricular tachycardia, *Am Jr Med Sci*, 1930, clxxix, 337-345
- ¹¹LEVINE, S A Clinical electrocardiography, Oxford Medicine, Oxford University Press, 370 (37)
- ¹²BARNES, A R, and WHITTEN, M B Study of the R-T interval in myocardial infarction, *Am Heart Jr*, 1929, v, 142-171
- ¹³LEVINE, S A, and FULTON, M N The effect of quinidine sulphate on ventricular tachycardia, clinical observations, *Jr Am Med Assoc*, 1929, xcii, 1,162-1,168

Control of the Tick Borne Diseases—Methods and Economics*

By NOXON TOOMEY, M D , F A C P , *Palmyra, Mo*

A SPECIES of tick was the first arthropod proved to be a vector of disease caused by microgametic life. The relation first discovered did not involve the human body, but that of cattle. However, the discovery did afford the foundation for suppositions, based on analogy, that were soon extended to the theory of infectious diseases in man, with results that have afforded a scientific insight into the transmission of a great many of the most serious infectious diseases of man.

Apart from any consideration of ticks as possible vectors of disease to man, the diseasecommunicating tick of cattle was at once recognized to be an economic liability of almost measurable degree. Efforts to free cattle of ticks, and to keep them free, became therefore an important and actively prosecuted problem of veterinary sanitation. Tick eradictory measures were consequently devised and studied in relation to cattle infestation, but were at first prosecuted only on the cattle grazing plains of the Southwest. For a long time the idea of tick control was virtually restricted to the requirements of profitable animal husbandry.

In 1902 a species of tick was sus-

pected by L. M. Wilson and Wm. M. Chowning as being the vector of spotted fever of the Rocky Mountains.⁹ Although their epidemiological investigations served to draw attention to the wood tick as a possible vector of spotted fever, they did not succeed in establishing the theory, which was tentatively accepted by John F. Anderson in 1903, but challenged and denied by Charles Wardell Stiles in 1904.²⁰

In 1904, Ross and Milne, in Uganda, and Dutton and Todd on the Congo River, discovered that the cause of African relapsing fever in man is a spirochete which is transmitted by the tick, *Ornithodoros moubata*, Murray.³⁴

In 1905, L. P. McCalla and H. A. Brereton transmitted spotted fever of the Rocky Mountains to man by means of tick bite (attachment) but their observations did not become generally known until they were published in 1908.

In 1906, W. W. King, and later in the same year, H. T. Ricketts transmitted spotted fever of the Rocky Mountains to guinea pigs.⁸³

With ticks proven to be a vector, and probably the sole vector of spotted fever, their important relation to that very fatal disease in the Bitter Root Valley of Montana became the

*Received for publication, September 2, 1931.

modulus for solving not only a very serious local health problem but a possible means for removing a very serious economic loss. The latter was entailed due to the justifiable fear of the disease entertained by old settlers and immigrants who refused to remain on the west side of the Bitter Root Valley. Thus hundreds of thousands of acres of exceptionally fertile land were kept from being settled and tilled uninterruptedly. The economic loss was so great that attempts at tick eradication in the Bitter Root Valley were anticipated as being profitable even at the expense of considerable experimentation and systematic, controlled efforts⁹³.

As a result, therefore, of economic pressure as well as humanitarian and public health considerations, there has been in Montana since 1911 a continuous scientific study and practical prosecution of tick control measures, with particular final reference to man, such as has never been attempted elsewhere. Thus, although we are indebted to veterinarians for the first studies directed at tick eradication, in its present day aspect we are almost entirely indebted to the Montana investigators and control officers for our current knowledge of the problems and methods involved in the control of the tick borne diseases^{92, 93, 94}.

Commenced initially with sole reference to spotted fever of the Rocky Mountains, the tick control program has become of constantly increasing significance in ratio with the number and importance of the several other diseases that have in recent years been demonstrated to be transmitted by

ticks, and to the evident widening dispersion of some if not all of them.

The diseases transmitted by ticks are spotted fever, tick paralysis, tularemia, American mountain tick-fever, certain indolent cutaneous ulcers of undetermined character, and, although apparently not in Montana or adjacent states, a relapsing fever of spirochetal origin.

Spotted fever, then considered to be cerebrospinal meningitis, was probably first described by Henry F. Hereford, M.D., of Gold Hill, Nevada, in Thomas M. Logan's article entitled "Report on the Medical Topography and Epidemic Diseases of California" published in the *Transactions of the American Medical Association* for 1866 (Vol. XVI, pp. 497-569). It was not however until the publications of Maxey, McCullough, Wilson and Chowning,⁹⁵ Anderson, and Craig¹⁷ that it became known to investigators as well as local physicians.

Tick paralysis was first described by Seymour Hadwen from British Columbia in 1914.¹ It was first recognized as being of concern elsewhere (Idaho and Montana) in 1923 by James Dade, chief inspector of the Idaho State Sheep Commission. The disease has been subsequently studied by R. R. Parker and W. J. Butler.

Although *tularemia* was first shown (by the studies of 1910 to 1915) to be transmitted by the bite of the blood sucking deer fly, *Chrysops discalis*, it was later, in 1923, proven to be transmitted also by the wood tick, *Deimantator andersoni*, according to demonstrations of R. R. Spencer and R. R. Parker.² The tick borne tularemia has also been studied by R. R. Parker, R. R. Spencer and Edward Francis.³

American mountain tick-fever was first described clinically in 1850 but without reference to being transmitted by ticks. Unaware of the earlier reports, Charles F. Kieffer in 1907 associated it with tick bites under the name of intermittent tick-fever. Since then it has attracted no notice except briefly in connection with spotted fever by F. E. Becker and by R. R. Parker, until the studies of the writer showed it to exist independently as a definite and distinct disease entity.^{8, 9, 10}

The tick borne relapsing fever of spirochaetal origin, first reported from Africa, has a related form in parts of North America (Texas) and probably in Mexico, a known vector being the tick *Ornithodoros turicata*.⁴

Thus there are in North America five well known specific diseases transmitted by ticks, and also certain indolent skin ulcers of unknown micro-gamic origin. But, as will be pointed out elsewhere, it is not to be supposed that a tick control (eradication) program of universal applicability can be worked out for all tick borne diseases and for all localities, as local circumstances and requirements differ very greatly, even radically. Hence each tick borne disease and tick infested locality will continue to have its own more or less peculiar problems, but whatever measures are successful in diminishing the incidence of a certain species, or family of ticks, will necessarily have some effectualness in reducing the prevalence of all the diseases transmitted by that species or group of species.

CONTROL MEASURES

Historically considered, tick control measures as related to the diseases

transmitted to man, had their inception in the general collective experience on the effect of avoiding certain localities at certain times of the year (avoiding exposure), and on the effect of the clearing of lands and of grazing, upon tick destruction.⁸⁸

The above mentioned measures being found helpful but not sufficient the first studies in Montana were devoted to rodent destruction and the application of the well known dipping of live stock as had been practiced for many years in the control of the tick fever of cattle.⁶⁷ The quarantining of stock, and the dragging for ticks were added, and rodent destruction became prosecuted in more ways.⁸⁵ Lastly have been the introduction of tick parasites,¹⁷¹ and the use of a vaccine for one of the diseases (the Spencer-Parker vaccine for spotted fever).^{169, 190}

The measures will be studied systematically rather than in their order of introduction. It will be observed, however, that the two sequences coincide to a considerable extent. In this connection it must be remembered that it was almost from the outstart realized that no one or two methods alone were dependable but that optimum results were to be arrived at by finding the combination of procedures that gave the lowest infected tick incidence for the cost involved.^{94, 95, 105} The methods available will be considered in the following order:

Avoidance of Exposure

Hygiene (frequent inspection) of person
Periodical exodus

Tick Destruction

Clearing land
Grazing
Dragging
Dipping of live stock

Quarantining of live stock
 Tick parasites
 Rodent Control

Trapping
 Shooting
 Poisoning
 Preventive Inoculation

Avoidance of exposure consists of systematic periodic search for ticks on the body and clothing of those who must enter infested districts, and the actual avoidance of infested areas during the tick season, the latter being from March 1 to July 15. Safety suggests, however, a removal out of infested districts from about February 15th to August 1st. The wearing of tick-proof clothing is helpful, but apt to be unbearable in summer time, and is at no time dependable, so should never lull the wearer into a false sense of security.

Where spotted fever is known to have a high mortality, periodical exodus of the rural population is still actually much practiced, but in the older control districts it is much less practiced than it used to be, and especially lately since the introduction of the spotted fever vaccine.

As to the conduct and value of these methods

Systematic periodical search for ticks on the body and clothing would be extremely valuable if carried out rigorously but the method is subject to the human elements of indifference, laziness and incompetence. Search should be thorough and at intervals not greater than twelve hours.

For thorough inspection individuals require assistance, hence it is best for groups to pair off so that each individual can have someone to act as assistant and inspector, this plan being additionally valuable in proportion to the mutual encouragement and

emulation it develops. The method is especially adapted for short camping trips and brief excursions into the mountains by trappers, range officers and lumbermen, but is often compromised by inadequate lighting facilities at night. Due to the human element, the method is impractical for prolonged periods, hence can not be included in a program devised for permanent residents. For health programs among tourists, campers and other casuals to infested districts, the twelve hour inspection and deticking method should be made the foundation of a prevention program. It has the advantage of placing no cost upon counties or the State, but does somewhat increase mental unrest. Periodical inspection is not of value against tularemia, American mountain tick-fever, the indolent ulcers, and spirochetal relapsing fever as a very brief period of attachment is sufficient to infect the individual with any one of those diseases, but for tick paralysis and spotted fever it is of value as attachment for about one and one-half hours is necessary for the tick to transmit spotted fever.

Detailed instructions concerning the character and arrangement of wearing apparel to diminish tick penetration, the habits of ticks, the preparation of camping grounds and sleeping arrangements, the search for and removal of ticks, and the treatment of tick bites has lately been published by R. R. Parker.²²⁴

Periodic exodus from infested districts during the tick season protects only for the time being and has no cumulative effect. It is economically expensive, but in dangerous uncontrolled districts it may be the only feasible method available.

Periodic exodus seems to have no appreciable effect in spreading ticks or the tick borne diseases, but it can not be denied that it has a slight tendency in that direction. It places virtually no direct expense on counties or the State but it does do so indirectly as it very noticeably depreciates business and the economic welfare of the areas affected. It contributes to mental unrest. Efforts should be made to make it unnecessary, and it should

not be part of an advertised program in a well controlled area, but as an emergency measure and for heavily infested areas that cannot economically support a control program the periodic exodus should not be discountenanced. During the period of exodus the method is of course effective for all of the tick borne diseases, but the method is, on an annual basis, not equally effective for all of the diseases as the mountain tick-fever, tularemia and perhaps tick paralysis are known to have a longer season than spotted fever, being not infrequently observed in August and occasionally in September.

We consider now the methods that largely comprise county or State control programs. They are methods that cannot for the most part be carried out effectually without county, State and even Federal assistance, coordination and control. They may be grouped under the headings of tick destruction, rodent extermination, and the use of prophylactic vaccination. All are necessary and economically justifiable for the most effective program in a thickly populated, heavily infested area but all are not equally available, economically, in thinly inhabited areas of low ground value ^{106, 116}

Tick Destruction

The clearing of land, especially in the more intensive types of farming, has a very marked effect in diminishing tick incidence but there is no reliable data as to what extent it does so. It has the unique advantage that it does not add an extra labor charge to the owners or tenants of farms, nor any additional cost to the county or State. It should be included as much as economic conditions warrant in any program for tick control.

Cattle grazing does not decrease tick incidence unless combined with dip-

ping. In fact without dipping it has some effect in increasing tick incidence and in spreading spotted fever ²¹¹. Combined with systematic and effective dipping it slightly decreases tick incidence.

Sheep grazing, at one time thought to be a valuable tick control measure, ⁷⁹ has been shown to be of only limited value ⁸¹. It is chiefly of service on uplands, where it has a definite place in the program due to the lessened applicability of other methods in those places ⁸⁸.

Dragging is a valuable method yielding quick results and particularly adapted for partially cleaning up small areas quickly. It does not have, however, sufficient cumulative effect to warrant a high labor charge. On the average, over a large project area the labor devoted to dragging should be kept to about one-fourth of that devoted to ground poisoning. It has the advantageous bi-effect of yielding thousands of ticks for experimental and other laboratory purposes such as the production of spotted fever vaccine.

The dipping of live stock is a useful method for tick control and yields results as quickly as dragging, but it also has no decided cumulative effect ⁸³. Granted proper facilities, the cost of dipping is not great compared to its value, but it has the disadvantage that it requires an appreciable capital outlay for dipping vats, and cannot in northern climates be invariably carried out as often as it should be, due to weather conditions. Dipping should be carried out preferably weekly, or at least every two weeks.

Dipping imposes some extra labor but farmers take to it readily provided the dipping vats are of convenient access. Beyond

the range of convenience there is noticeable indifference to dipping, the hand picking of ticks from cattle being more popular¹⁸⁷

Stock dipping can not be carried out as economically under semi-range and foot-hill conditions as where the area is entirely range land. However the dipping of live stock in infected areas has a definite place in tick control as it is available in foot-hill country where rodent control cannot be so successfully practiced. In those places wild animal life meets with domestic animal life and it naturally follows that dipping will do more good in such districts, although the amount of good it does in such districts is questionable²¹¹

The practice in Montana is to exempt milch cows from dipping provided the owner keeps them free from ticks by hand picking or by spraying with an arsenic-pine tar solution containing 0.22% arsenic trioxid

Dermacentor andersoni appears to be somewhat more resistant to arsenical dips than the cattle tick, and so it has been found best to add a soft soap-kerosene emulsion to the arsenical, following the Watkins-Pitchford formula⁶. By this addition the destructive effect of the material on the tick is increased and the caustic action on the host is reduced. This formula is as follows, English measure: Arsenite of soda (80 per cent arsenious oxide), 8.5 lbs., soft soap, 5.5 lbs., kerosene oil, 2 imperial gallons, water, 400 imperial gallons. It is important that the proper strength of the solution be maintained at all times, both to secure efficiency in tick destruction and to avoid injury to the stock⁶. A simple outfit has been devised by the U. S. Bureau of Animal Industry for determining the percentage of arsenic present⁷.

The quarantining of stock during the tick season does not reduce the incidence of ticks in the infested areas. The measure was introduced to prevent the mechanical carrying away of ticks from dangerous areas, in that respect it is undoubtedly very successful. Animals that must be shipped during the tick season are released from quar-

antine only after being dipped and inspected by a state officer for freedom from ticks^{187, 211}

The cost of enforcing quarantine is nil or very trifling as the duty of enforcing it is merged with the duties of the brand inspectors.

Tick Parasites

The high mountain reaches being the fountain head and impregnable fortress of both ticks and wild animal life, they are unassailable by the control measures already mentioned, including the rodent control measures to be mentioned. Hence a new method is necessary that will offer some prospects of destroying ticks above the foot-hills¹⁸³. In hopes that they might find the ticks in their inaccessible abodes, the tick parasite, *Ixodiphagus caucurtei* du Buysson, a minute chalcid fly was imported into America from France in 1926¹⁸⁴.

A great deal of work has been done by Cooley, Morton and Kohls on studying the tick parasite, *Ixodiphagus caucurtei*, with particular reference to its artificial propagation,¹⁸⁵ its suitability for the climate of Montana, and its liberation at strategic points¹⁸⁶.

The chalcidoid fly has been reared in large quantities by the Montana State Board of Entomology in its laboratory at Hamilton, Montana. These minute flies have been liberated to the extent of about two million specimens during the past four years (1927 to 1931). Twelve colonization areas have been selected in western Montana and seven in eastern Montana. In 1929, one year after the release of 82,200, in the Lick Creek area, 250 engorged nymphal ticks were secured from 108 squirrels. Upon incubation it was found that 14 (7.5 per cent) of the ticks were parasitized. Equally encouraging results were not obtained in 1930, but the data obtained were too limited¹⁸⁷.

warrant the drawing of conclusions. Although it is much too early to determine what will be the ultimate value and results of tick parasite liberations it may be said that all theoretical considerations and practical observations are distinctly encouraging at the present time. Obviously it is impossible to equate cost with results at this time but the work being done along the line of tick parasites has the very great advantage that it is constructive and cumulative in value, and is available in regions where other methods of tick control are not available.

Rodent Extermination

The shooting of rodents should be encouraged by permitting an open season at all times as far as rodents are concerned. Shooting does not, however, sufficiently reduce the incidence to warrant the paying of a bounty unless of a very trifling character. It should be an incidental but not a main effort of county and state employees as it is not sufficiently productive of permanent results to justify the cost of time and material required.

Trapping, likewise, should be a method available to the public at all times, and one employed by control officers incidentally to other field work. It does not kill enough immature animals to have much cumulative effect, hence does not warrant a high labor cost or the paying of more than trifling bounties.

Shooting and trapping are of most value for clearing up very small areas for brief periods, and are of chief applicability for certain points with a brief tourist season.

Rodent extermination by means of poison has the most cumulative effect as it kills the fair proportion of immature animals before they have opportunity to breed. It is not, however, as productive of quick results as are shooting and trapping. Poisoning of

lands can not be carried out discursively for best results but should be carried out in a planned and systematic manner, extending concentrically from strategic points. The use of poison is especially adapted to plains and low foot-hill areas but is not feasible for mountain sides. The poison placed on or near grazing lands occasionally kills live stock as well as rodents, hence farmers are at first usually actively opposed to its use. It can be shown, however, that the loss entailed is comparatively trifling. Where there are means for compensating farmers for their loss, opposition to rodent control by means of poison becomes less in time as eventually the farmers' live stock is considerably improved by being kept free from ticks.

The Montana experience has been that of 41 cases of stock poisoning reported in the seven years 1923 to 1930 (over an area of about 425 square miles) investigation resulted in a settlement being made in 20 (about one-half) of the cases. The average per annum cost of settlement for the five years 1924 to 1929 was \$120, and represented the loss of six horses, eight cows, nine pigs, nine sheep, and four geese for the five-year period, or about three large and four small animals per year. The above low loss of stock and cost to the State could not have been accomplished, however, without experienced labor in placing the poison and without careful investigation of claims (including toxicologic analysis of viscera of allegedly poisoned animals). Since strychnine has lately been replaced by calcium cyanide under certain circumstances, the loss of live stock will be still less ^{170, 189}

The effect of the systematic annual and partly semi-annual use of poison in the Hamilton to Missoula, Florence, and Lolo districts of Montana has been to reduce the rodent population as observed on a measured trip (at the same time of the year) from 194 in 1924 to 16 in 1930.

The cost (time and material only) of rodent control by poison has averaged \$0 02681 per acre per year for the four year period 1927 to 1931. This is equivalent to a cost of \$5 362 per year for a 200 acre farm, or \$26 81 for a five year period. After the latter has been established the control by poison can be maintained for about \$5 00 per year, or \$2 50 per 100 acres if done intelligently, systematically and on a large enough scale.

The combined amount of land treated in the Ravalli County and Missoula County control areas in 1927 was 246,697 acres and in 1930, 271,533 acres. The latter is equivalent to about 425 square miles or a strip eight miles wide by 53 1 miles long. The average total annual cost for the area was \$7,280, representing a labor of 1,456 eight-hour days or the employment of sixteen men for ninety-one days a year. The average number of baits per acre were 4 02 for Ravalli County and 1 22 for Missoula County. A trifle over one-third of the land was poisoned twice a year. The amount of materials used in 1930 were 6,686 quarts of poisoned grain and 5,261 pounds of calcium cyanide.

The poisoned grain is made by mixing crushed whole oats, 40 quarts, with a solution of molasses (4 pints of molasses and one and one-half quarts of water) in which has been dissolved a mixture of strychnine, 5 ounces, saccharine, 5 drams, gloss starch, 2 5 lbs., and sodium bicarbonate, 5 ounces. The dry powders are first mixed together and then dissolved in the warmed solution of molasses. The whole is then poured over the oats and rapidly mixed by hand. Rubber gloves should invariably be worn and the hands thoroughly washed after mixing the poison into the grain. The grain-poison mixture is then spread on canvas or muslin racks until it is thoroughly dry.

About one teaspoonful is placed usually on the surface of the ground at the rear of the rodent's hole or burrow. It should be either spread out over the ground or placed in a small shallow depression where it will be accessible to the rodents but not attract the attention of large domestic animals.

Prophylactic Vaccination

Recognizing that tick eradictory methods and rodent control measures

were but partially successful at best, even when intensively practiced, and that no method except the frequent periodic inspection of the body for ticks was available against spotted fever in areas beyond the controlled areas, the desirability of artificially immunizing people against spotted fever was at once apparent. Accordingly, R. R. Spencer and R. R. Parker at the Montana Laboratory for the Study of Insect-Borne Disease, Hamilton, Montana, developed a vaccine of considerable protective value against spotted fever. The vaccine is prepared solely by the U. S. Public Health Service at Hamilton, Montana.

At present spotted fever is the only tick borne disease for which there is a method of prophylaxis by means of inoculation.

The vaccine for active immunization against spotted fever is of the attenuated virus type. It is to be used before the tick season in two doses with a week's interval between doses. It should be repeated annually. The annual inoculations seem to have a slight cumulative effect.

About twenty-five thousand persons have been inoculated with the vaccine during the period 1925 to 1931 inclusive. Each year there has been an increasing demand for the vaccine and it has been necessary to increase production accordingly. The amount manufactured was doubled in 1929, again in 1930, and again in 1931. The heaviest call is from Montana, Wyoming, Idaho, and Oregon, the last named state using the most in 1930.

From the results of a two year test (1926 and 1927) made in southern Idaho against the mildest type of the disease and another test against the most virulent type, which had been in progress for four years in the Bitter Root Valley, the following conclusions were expressed—that against the milder type of

infection the vaccine usually afforded full or nearly full protection, while against the highly virulent type the degree of protection was usually sufficient to cause a marked amelioration of the customary very severe symptoms and to insure the recovery of most cases. No further test was deemed necessary so far as the mild types were concerned, but additional data seemed desirable in regard to efficacy against the virulent type. Therefore, complete record keeping in the Bitter Root Valley has been continued. The full six years' data for this valley (1925 to 1931) show that since the beginning of the test 3,578 persons have been vaccinated, of which nine have received vaccine in six different years, 64 in five years, 143 in four years, 257 in three years, 555 in two years, and 2,550 once. During this test period 46 persons have become infected with the highly fatal local strains. Of these, 30 were in non-vaccinated persons and 16 among those vaccinated. Of the 30 nonvaccinated cases, 22 died, of the 16 vaccinated only three. The death rate in the former group was 73.33, in the latter 18.75, thus showing a marked reduction in mortality in favor of the vaccinated cases.²⁰⁰

The cost of manufacture of the vaccine has been thought to make its manufacture commercially infeasible. While this fact was undoubtedly true in the experimental stage, there seems reason to suppose that with demonstrated value, and larger production, the manufacture can now be put on a commercially justifiable basis.

COMPARATIVE ECONOMICS

Total economics cannot be given accurately at the present time as a true pro rata cost of the tick parasite efforts and the prophylactic vaccination campaigns cannot be more than approximated.

Of known costs, rodent control by poisoning of land places an average charge of \$5 per 200 acres, dragging about one-fourth as much again, dipping about one-half as much again and general overhead and administration

charges for these control measures, an additional one-fourth so that the annual charge for these measures is about \$10.00 per 200 acres (or average farm family), the per capita cost being about \$2 per year. Assuming vaccination to be on a commercial basis it could under average conditions be carried out on a cost basis for about one dollar a year for urban inhabitants and two dollars a year for rural inhabitants, assuming organized effort and full cooperation of the inhabitants in reporting to conveniently placed temporary stations (physicians' offices, public health booths, etc.).

Thus for all tick and spotted fever control measures other than the tick parasite investigations there is in heavily infested but well controlled areas an annual cost (averaging rural with urban) of about \$3.50 per capita or \$17.50 per average family on a 200 acre farm or \$8.75 per 100 acres. General research work would bring this up to \$10.00 per 100 acres per year. Compared with many other reclamation projects (drainage districts, irrigation districts, etc.) this is not an economically unjustifiable charge for land of good average productivity, although it must be remembered that it is not a temporary charge for a permanent or semi-permanent improvement but is an indefinitely necessary annual charge with only slight to moderate cumulative effect, and none that would endure more than briefly if all control efforts were relaxed.

The above costs are obtained under reasonably favorable conditions. Under but slightly less favorable conditions they might be two, three, or four times as great. Hence, unless land is of ex-

ceptional economic value it can not afford to carry the burden of much control work of present type spent on difficultly controlled adjacent uplands of low economic value. Also, it should be remembered that initial efforts are always more expensive than subsequent maintenance efforts. Hence an initial three to five year tick control program would have to provide an average annual charge of perhaps \$12 to \$14 per 100 acres, and under some conditions (transportation facilities, etc.) even more. Mountain sides and other timber land obviously cannot bear one-tenth such a cost, and yet they are the fountain head, and so far unassailable fortress, of tick life. It is on account of these considerations that efforts towards propagating tick parasites are so very important. On the other hand, if an individual can be effectively immunized against a tick borne disease, the concern as to tick incidence is proportionately reduced, at least as far as that disease is concerned.

Where dangerously infected areas have a recreational appeal of a dispersive sort it should be the policy of the responsible control officer of the area to close certain parts of the dangerous area to the public, which will thereby concentrate recreational activities in a locality or localities that can be controlled with fair prospects and economic justification.

RESULTS OF TICK CONTROL MEASURES AS TO REDUCING MORBIDITY IN MAN

Tick control measures have decided value in relation to improving animal husbandry (tularemia, tick paralysis, etc.) and these valuable by-effects should be kept in mind. The purpose

of this article is, however, to consider only the demonstrated effect of tick control measures in reducing disease in man.

Spotted fever as existing in the Bitter Root Valley affords a valuable yardstick on account of the reliable statistics that have accumulated on the subject during the past thirty years.

From 1913 to 1929 there were 113 cases of spotted fever in Missoula, Ravalli and Granite Counties (the Bitter Root Valley) Montana. Of these, 48 cases (42.5 per cent) occurred in the older control districts of the Florence, Stevensville, Victor, Hamilton and Gold Creek areas, all in Ravalli county.^{21,2} In these areas combined, the following number of cases occurred

In 1913 and 1914	14
1915 and 1916	7
1917 and 1918	0*
1919 and 1920	5*
1921 and 1922	8
1923 and 1924	6
1925 and 1926	3
1927 and 1928	2
1929 and 1930	1

*The reduction in these years was very probably largely due to the diminished male population on account of the men being away in army service during the World War.

Comparing the quadrennium 1913-1916 with its 21 cases against the quadrennium 1927-1930 with its 6 cases we find a reduction of morbidity in these areas from 100 per cent to 28.6 per cent (actually the reduction was to under 25 per cent of the old uncontrolled rate, as the first four years, 1913-1916, showed some effect of tick control measures).

On the same basis, for the whole valley the reduction would be from 38 cases in 1913-1916 to 10.87 cases in

1927-1930, or 27 cases less during a four year period. As the death rate for all unvaccinated cases in this valley has for thirty years been 76.81 per cent, it is safe to say that of the 27.13 fewer cases, 20.84 cases (76.81 per cent) represent lives saved, or a trifle better than five a year. Placing for economic purposes a nominal value of \$2,500 per average human life, this would represent a saving of \$13,000 a year, which with \$2,000 for critical illness and temporary loss of earning power, for six others, would in an economic way well balance the total known cost of control measures, which was on the average of ten cents per acre for an average of about 150,000 acres (well under that number before 1927, up to 271,500 since then) or about \$15,000 a year.

While these figures do not represent any "juggling" it is not to be understood that they are meant to represent more than an *approximate* appraisal of economic results. At that, however, they do indicate that even on a crass economic basis it is evident that all moneys spent for tick control measures have been spent justifiably, on a human morbidity-mortality basis alone.

In addition there has been, besides improvement in quality of live stock, an enhancement in land values that alone would have more than justified the cost of all tick control measures. Thus it is safe to say that over an eighteen year period of tick control, the fundamental land values of the Bitter Root Valley have appreciated at a rate greater than an annual average of \$50,000.

To the known savings effected in connection with spotted fever should be added the diminished incidence of the other tick borne diseases. The amount of diminution of the latter is not known, as only recently have tularemia and tick paralysis been recognized in man, and the American mountain tick-fever has not attracted attention in the Bitter Root Valley in recent years. As already remarked, the distribution of the tick borne diseases varies somewhat according to locality, hence a tick reduction program elsewhere might not be as economically productive of good as it has been in the Bitter Root Valley, even though the other tick borne diseases were almost totally eliminated, as collectively they do not seem to be of an economic importance equal to that of spotted fever.

REFERENCES

The numbers indicate the chronological sequence of the papers in a complete bibliography of spotted fever compiled by the author.

⁶WILSON, L. B., and CHOWNING, WM. M. Spotted fever of Montana. Northwest Lancet, 1902, xxii, 440-442, and Med Sentinel, 1902, x, 238-239.

¹⁷CRAIG, CHAS. F. The relation of the so-called "*Piroplasma hominis*" and certain degenerative changes in the erythrocytes. Am Med, 1904, viii, 1016-1017.

²⁰STILERS, C. W. Preliminary report upon

a zoological investigation into the cause, transmission, and source of the so-called spotted fever of the Rocky Mountains. 2d Bien Rep Montana St Bd Health, 1905, Pp 160-162.

³⁴ALLBUTT, C., and ROLLESTON, H. D. A system of medicine by many writers, 1910, London, Macmillan and Co. Articles: Tick fever by Mr P. H. Ross, and Spotted fever of the Rocky Mountains by Dr L. W. Sambon. Vol II, Part II, 301-306, 307-313.

⁶³RICKERTS, H. T. Investigations of the

- cause and means of prevention of Rocky Mountain spotted fever carried on during 1907 and 1908 4th Bien Rep Montana St. Bd Health, 1909, Pp 77-191
- ⁶⁷HENSHAW, W H, and BIRDSEYE, C The mammals of the Bitter Root Valley, Montana, in their relation to spotted fever Circular No 82, Bur Biol Survey, U S Dept Agric, 24 pp
- ⁶⁸HUNTER, W D, and BISHOPP, F C The Rocky Mountain spotted fever tick with special reference to the problem of its control in the Bitter Root Valley in Montana Bull No. 105, Bur Entomol, U S Dept Agric, pp 47
- ⁷⁰McCLINTIC, THOMAS B Investigations of, and tick eradication in, Rocky Mountain spotted fever U S Public Health Rpts, 1912, xxvii, 732-760
- ⁸¹WOOD, H P Sheep grazing as a means for tick destruction U S Dept of Agric Bull No 45, 1913, Pp 1-11
- ⁸²NUTTALL, G H F, and WARBURTON, C Ticks a monograph on the Ixodoidea, Cambridge Univ Press, 1908-1915
- ⁸³CHICAGO PATHOLOGICAL SOCIETY Contributions to medical science by Howard Taylor Ricketts, 1870-1910, Univ of Chicago Press, 1911, 278-450
- ⁸⁶COOLEY, R A Tick control in relation to the Rocky Mountain spotted fever Montana Agric Coll Exp Sta Bull No 85, Bozeman, 1911, Pp 1-29
- ⁸⁸FRICKS, LUNSFORD D Rocky Mountain spotted fever Sheep grazing as a possible means of controlling the wood tick (*Dermacentor andersoni*) in the Bitter Root Valley U S Pub Health Rpts, 1913, xxviii, 1647-1653
- ⁹⁰MAXBY, ED E Rocky Mountain spotted fever Forscheimer's therapeutics of internal disease, 1913, II, 562-569 New York, Appletons
- ⁹²KING, W V Work of the Bureau of Entomology against spotted fever in co-operation with Board 1st Bien Rep Montana St Bd Entomol, 1915, 16-27
- ⁹³FRICKS, LUNSFORD D A review of Rocky Mountain spotted fever eradication work conducted by the U S Public Health Service in the Bitter Root Valley 1st Bien Rep Montana St. Bd Entomol, 1915, 16-27
- ⁹⁴FRICKS, L D Rocky Mountain spotted fever A report of its investigation and measures undertaken for its eradication during 1914 U S Pub Health Rpts, 1915, 148-165, 516-521, 1694
- ⁹⁵COOLEY, R A The spotted fever tick (*Dermacentor venustus* Banks) and its control in the Bitter Root Valley, Montana—a review Jr Econ Ent, 1915, viii, 47-53
- ¹⁰⁵KING, W V Report on the investigation and control of the Rocky Mountain spotted fever tick in Montana during 1915-1916 2d Bien Rep Montana St. Bd Entomol, 1917, 13-23
- ¹⁰⁰FRICKS, L D Review of Rocky Mountain spotted fever eradication work conducted by U S Public Health Service in Bitter Root Valley, Montana, 1915-1916 2d Bien Rep Montana St Bd Entomol, 24-34
- ¹¹⁶PARKER, R R Tick control program for 1919 Circ No 1, Montana St Bd Entomol, 1919, 1-23
- ¹³³COOLEY, R A The spotted fever tick, *Dermacentor* [sic] *venustus* Banks Sp Bull No 26 Montana St Bd Health, 1923, 9-15
- ¹³⁷BUTLER, W J Control methods in the repression of spotted fever Sp Bull No 26 Montana St Bd Health, 1923, 28-32
- ¹⁰⁹SPENCER, R R, and PARKER, R R Prophylactic vaccination against Rocky Mountain spotted fever 6th Bien Rep Montana St Bd Entomol, 1927, 28-32
- ¹⁷⁰O'DONNELL, FRANK J Control work Rocky Mountain spotted fever control districts, Bitter Root Valley, for the period Jan 1, 1923 to Dec 31, 1926 6th Bien Rep Montana St Bd Entomol, 1927, 41-54
- ¹⁷¹COOLEY, R A "Tick parasites" Med Sentinel, 1927, xxxv, 805-815
- ¹⁸³COOLEY, R A Tick parasites—executive report 7th Bien Rep Montana St Bd Entomol, 1929, 10-16
- ¹⁸¹COOLEY, R A Preliminary report on the tick parasite, *Ixodiphagus caucurtei* du Buysson 7th Bien Rep Montana St Bd Entomol, 1929, 17-31
- ¹⁸⁵MORTON, FRED A Quantity production of tick parasites 7th Bien Rep Montana St Bd Entomol, 1929, 32-35

- ¹⁸⁶PARKER, J R, and BUTLER, W J Tick parasite liberation in Montana during 1928 7th Bien Rep Montana St Bd Entomol, 1929, 35-38
- ¹⁸⁹O'DONNELL, FRANK J Control work Rocky Mountain spotted fever control districts, Bitter Root Valley, 1927-1928 7th Bien Rep Montana St Bd Entomol 1929, 70-76
- ¹⁹⁰PARKER, R R Vaccination against Rocky Mountain spotted fever 7th Bien Rep Montana St Bd Entomol, 1929, 68-69
- ²⁰⁹PARKER, R R Present status of the use of Public Health vaccine for Rocky Mountain spotted fever 8th Bien Rep Montana St Bd Entomol, 1931, 36-38
- ²¹¹BUTLER, W J Review of dipping and quarantines 8th Bien Rep Montana St Bd Entomol, 1931, 38-40
- ²¹²O'DONNELL, FRANK J Control work Rocky Mountain spotted fever control districts, Bitter Root Valley, for the biennium ending December 31, 1930 8th Bien Rep Montana St Bd Entomol, 1931, 40-44
- ²²⁴PARKER, R R Rocky Mountain spotted fever and other diseases caused by the bite of the Rocky Mountain spotted fever tick within the limits of the Northern District of the Bureau of the Forest Service [Hamilton, Mont], 1-8

COLLATERAL REFERENCES

- ¹HADWEN, SEYMOUR On "Tick Paralysis" in sheep and man following bites of *Dermacentor venustus*, with notes on the biology of the tick Parasitology, 1914, vi, 283-287
- ²PARKER, R R, and BUTLER, W J Results of preliminary investigations in Montana of pathological conditions in sheep due to the wood tick, *Dermacentor andersoni*, Stiles 7th Bien Rep Montana St Bd Entomol, 1929, 77-85
- ³PARKER, R R, SPENCER, R R, and FRANCIS, EDWARD Tularemia infection in ticks of the species *Dermacentor andersoni*, Stiles, in the Bitter Root Valley, Montana U S Pub Health Rpts, 1924, xxxix, 1057-1073
- ⁴WELLER, BURFORD, and GRAHAM, G M Relapsing tick-fever in Texas Jr Am Med Assoc, 1930, xcvi, 1834-1835
- ⁵WATKINS-PITCHFORD, R Dipping and tick destroying agents Agr Jr Union of S Africa, 1911, ii, 33-79
- ⁶CHAPIN, R M Arsenical cattle dips U S Dept Agr Farmers' Bull 603, 16 pp
- ⁷CHAPIN, R M Laboratory and field assay of arsenical dipping fluids, 1914, U S Dept Agr Bull 76, 17 pp
- ⁸TOOMEY, NOXON Mountain fever and spotted fever of the Rocky Mountains—Clinical studies ANN INT MED, 1931, v, 585-600
- ⁹TOOMEY, NOXON American mountain tick-fever and spotted fever of the Rocky Mountains—Comparative epidemiography ANN INT MED, 1931, v, 601-612
- ¹⁰TOOMEY, NOXON American mountain tick-fever Semeiography and nosology ANN INT MED, 1932, v, 912-923

The Etiology of Colds*

By JOHN E. WALKER, M.D., *Opelika, Alabama*

THERE is a growing conviction that colds are due to a specific filtrable virus. This conclusion is of such importance that the evidence leading up to it needs to be examined critically. The evidence in favor of the view is two-fold. First, experiments have been reported which appear to show that colds can be transmitted to humans and to chimpanzees by bacteria-free filtrates of nasopharyngeal secretion obtained from persons suffering from colds. Secondly, it is supposed that there is sufficient evidence to show that ordinary bacteria, while admitted to be pathogenic, are in no way concerned in the primary etiology of colds. It is the purpose of this paper to consider the nature of this dual evidence.

TRANSMISSION EXPERIMENTS WITH FILTRATES

The experimental method relating to the transmission of colds with bacteria-free filtrates of nasopharyngeal secretions is simple in principle. The filtrate is instilled into the nasopharyngeal passages of volunteers who are kept under observation to determine whether or not they develop a cold. The interpretation of results however is full of pitfalls, for there are no cri-

teria of successful transmission other than clinical symptoms. These clinical symptoms are very indefinite both in kind and in degree. Anything between a transient nasal discharge and pneumonia may be so classified, possibly correctly so far as we know at present. No one would attempt to define the severity of headache, the amount of sneezing, the degree of hyperemia of the mucous membranes, the severity of sore throat, or the volume of nasopharyngeal secretion necessary to establish the diagnosis of a cold, or even to say which of these symptoms need be present. Yet, it is solely on such symptoms that the interpretation of transmission experiments depends. Experimenters cannot protect against error by disregarding mild symptoms, this recourse would still leave the etiology of mild colds unsolved.

Further, suggestion plays a great part in the subjective (possibly also the objective) symptoms of the volunteers. Only those who have served as subjects for such experiments, as I have done, know fully the potent influence of this factor. The curiosity and expectation are intense, every breath is carefully drawn in to detect possible nasal obstruction; every sneeze is followed by an anxious waiting period for other sneezes.

Dochez¹ and his co-workers found

*Received for publication, November 20, 1931

this factor of suggestion so powerful that it was necessary to use "various ruses, such as nasal injections of sterile broth, collection of nasal washings for culture and equivocal statements" in order to keep the subjects in ignorance. One of their subjects in particular appeared willing to develop or not to develop a cold according to what he thought was expected of him. Also, he was willing and anxious to change his symptoms if he thought that his first impression was an error. In view of these considerations, and the well known tendency of humans to develop respiratory symptoms at any time, it is extremely doubtful whether such symptoms¹ as a mild cold "in which sore throat, laryngitis and cough with a moderate amount of sputum were conspicuous" or "a simple uncomplicated mild cold" can be given sufficient weight on which to form a final judgment. This is particularly the case, since no volunteers submitted to the same psychic influences were reserved as controls.

Long² and his group also recognized the possibility of error as a result of the psychic reactions of the subjects. During a five day period the subjects were given several nasal instillations of broth in order to keep them in ignorance. Yet, at the end of this time, they all received instillations of filtered nasopharyngeal secretions. The control group was the general population of Baltimore, persons living under entirely different conditions, not elaborately hospitalized like the volunteers, and certainly not subjected to "careful examinations of the nose and throat by several observers" as soon as they complained of symptoms.

Besides the factor of suggestion, the interpretation of symptoms following the nasal instillation of filtrates is rendered all the more difficult since, as stated by Dochez,¹ the filtrates are irritating to the mucous membranes and cause in "practically all cases, negative and positive, some slight stuffiness of the nose, a little sneezing, and occasionally slight headache." This is further complicated by the fact that the subjects received intranasal instillations of broth, likewise irritating, in the days immediately preceding the test inoculations. No one apparently has attempted to determine the effect of this repeated instillation of irritating liquids on nasal symptoms in humans. The powerful effect of irritating chemicals in causing nasal symptoms in rabbits was shown by Carrol G. Bull.

The great importance of this subject for human welfare requires that such experiments be better controlled. Larger groups should be used, say 50 to 100, with an equally large control group. It is obviously unnecessary to hospitalize these persons if they are kept under the same living conditions. Preliminary broth injections are also unnecessary in an adequately controlled experiment. However, the subjects and also the observers responsible for the diagnosis of colds should be in complete ignorance as to the nature of the instillations used. I know of no place where such an experiment could be satisfactorily performed outside of the military service.

Unfortunately, such an experiment even with a markedly significant difference between experimental and control groups would not settle the problem by proving that colds are due to a filter-

able virus There is another objection to be answered Filtered nasopharyngeal secretions contain a number of substances in solution, substances derived from micro-organisms as well as of human origin It is more than a theoretical possibility that the coryzas following the nasal instillation of such substances represent an allergic response by the nasal mucous membrane There is no more reason to consider the coryzas produced by such instillations as due to a filtrable virus than there is to consider the ophthalmic reaction following the instillation of minute traces of tuberculin as due to a filtrable virus The nasal mucosa is more apt to respond to foreign substances by allergic reactions than any other tissue of the body The absence of a specific skin reaction to the nasopharyngeal filtrates would not influence the question These views regarding the possible allergic nature of the coryzas following the nasal instillations of filtered nasopharyngeal secretions were expressed ten years ago by Victor C Vaughan,³ though as far as I can determine none of the proponents of the filtrable virus theory has made any effort whatever to take them into consideration

Experiments⁴ have been recently reported regarding the possible cultivation of this hypothetical virus It is to be noted that the authors were properly conservative in their claims saying "we realize the difficulty of a final judgment concerning the successful cultivation of an invisible agent and simply present the facts as we have observed them" The experimental method was, of course, exactly the same as that discussed above, the only difference being that here the "virus" was obtained

from a test-tube instead of directly from the nasopharynx The same objections regarding interpretation likewise apply

In short, the filtrable virus theory of colds is not only unproved, but even if correct, it appears impossible to prove it with the means at present at our disposal

THE HYPOTHESIS THAT COLDS ARE NOT DUE TO ORDINARY BACTERIA

Another series of experiments by Shibley,⁵ Hangar, and Dochez, is commonly cited as demonstrating that bacteria can no longer be considered of importance in the primary etiology of colds In these experiments normal individuals were studied over a long period, and changes occurring in the respiratory flora during the development of colds were noted The authors⁶ state that "from the results of this study we were led to conclude that none of the aerobic organisms is of primary etiologic significance because none appears for the first time in significantly increased numbers during the early days of a cold Later they may be present as important secondary invaders" But lateness of appearance of an organism in artificial culture does not *ipso facto* displace the organism from the position of primary etiology This point can be demonstrated by reference to two observations that have been made by me

1 A⁷ culture of *B. Pfeifferi* was accidentally sprayed over the face of a laboratory worker A severe upper respiratory infection followed, characterized by watery nasal secretion, bronchitis and conjunctivitis Late cultures made from the exudates showed myr-

iads of organisms serologically identical with the organism inoculated. These positive late cultures contrasted strongly with the fact that an early culture made, however, at a time when symptoms were well established, was entirely negative for this organism. This observation is in many respects similar to a spontaneous cold recorded (Case 1, K C M) by Shibley⁵ and his co-workers and on which their conclusion already referred to was partly based. K C M showed no Pfeiffer's bacilli on nasal culture when symptoms first appeared. Later nasal culture showed a pure growth of this organism. Most probably K C M's cold was caused by *B. Pfeifferi*, exactly as there is no reason to doubt that this organism was responsible for the infection recorded by me.

2. A⁸ dilute culture of *Micrococcus catarrhalis* was purposely inoculated into the nose. A cold characterized by watery nasal secretion, sneezing, and later mucoid nasal secretion followed. Cultures of the mucoid nasal secretion showed many colonies of *M. catarrhalis*, although a previous culture of the early watery secretion had been entirely negative for this organism. I was the subject myself for these two observations. I make no claim of absolute freedom from disturbing psychic reactions. However, the inoculation of cultivatable bacteria and the later recovery of these bacteria by culture are concrete facts, for which there is no parallel in filtrable virus experiments.

It is not surprising that the thin watery secretion which often characterizes the early stages of a cold should contain few or no organisms. The situation is probably similar to that in

which only a few pollen granules are necessary to produce an attack of hay fever. No one, of course, would contend that the extrinsic factor in hay fever is not pollen merely because pollen cannot be demonstrated in the nasal discharge. Nor would anyone consider that hay fever was due to a virus if it should be demonstrated that the filtered nasopharyngeal secretion of one victim caused symptoms when instilled into the nasal cavity of another susceptible person. The mechanism of colds is possibly very similar to the mechanism of hay fever, with the exception that the causative agent in the case of colds is capable of multiplication, of actual invasion of the tissues, and of giving rise to a purulent exudate in some instances.

The experiments with chimpanzees, reported by Dochez¹ and his co-workers, also bear certain points of resemblance to the two observations made by me. These animals were inoculated with filtered nasopharyngeal secretions, and seven of sixteen animals so inoculated developed colds. This observation is cited by Dochez as further evidence supporting the filtrable virus hypothesis. But the animals developing colds showed a great increase in pneumococci or *B. Pfeifferi* on culture of the nose and throat as the colds progressed. I feel that it is much more logical to attribute the colds to these organisms rather than to postulate a virus in the filtrates. An adventitious origin of the colds cannot be excluded, particularly since these animals are very susceptible to such infections. Although eight control animals did not develop colds, it is to be noted that the work with the controls was done in June and July⁹.

while the filtrates were inoculated in the test animals in winter. Obviously, the controls are not strictly parallel. Further, as in the case of the human experiments with filtrates, the possibility of an irritating or allergic reaction caused by the filtrates and paving the way for later bacterial invasion was not taken into consideration.

A great lacuna in this work with chimpanzees is that none of them has been inoculated with ordinary respiratory bacteria. My own experience with laboratory infections due to respiratory bacteria convinces me that the resulting cold may be too cruel and too severe for any widespread use of human beings for this purpose. It appears permissible, however, to inoculate humans with diphtheroids and *M. catarrhalis*, preferably such organisms as have not had many generations on artificial media.

The two observations mentioned above relating to the development of colds in humans following the intranasal inoculation by no means exhausts all instances of this kind. I have recorded a second infection due to *M. catarrhalis*, and still another¹⁰ resulting from *B. bronchisepticus*. I was also the subject of these experiments. But the literature is replete with other examples cited, among others, by Park and Cooper,¹¹ by Cecil and Steffen,¹² and by Fenyvessy and Kopp.¹³ In the presence of this mass of evidence it seems unjustified to conclude that we need no longer concern ourselves with the possibility that ordinary bacteria may be the primary etiological agents of colds.

SUMMARY

The reported experiments relating to the hypothesis that colds are due to a filtrable virus are inadequate to support the hypothesis. Such disturbing factors as difficulty in diagnosis, the influence of suggestion on the subjects, the irritative properties of the filtrates on the nasal mucosa, and the possible presence of allergic reactions to the filtrates have not been properly controlled. With the means at present at our disposal it is even doubtful whether the hypothesis can be submitted to proper experimental test.

The filtrable virus hypothesis rests on another hypothesis, namely, that ordinary respiratory bacteria are not concerned in the primary etiology of colds. This underlying hypothesis is likewise unproved. Two personal observations are cited which demonstrate that causative bacteria may be absent in early cultures made from the exudate in colds. These, and other instances from the literature, favor bacteria as being the extrinsic factor in the etiology of colds.

The early reaction in colds is probably very similar to the hay fever reaction to pollens. The difference consists in the fact that the etiological agent of colds (bacteria) possesses the power of multiplication and of tissue invasion. Later they may give rise to a purulent exudate. The etiological agent may be very numerous in culture only in this purulent exudate. The late appearance of bacteria in cultures does not prove that they are merely secondary invaders.

REFERENCES

- ¹DOCHEZ, R R , SHIBLEY, G S , and MILLS, K C Studies in the common cold IV Experimental transmission of the common cold to anthropoid apes and human beings by means of a filtered agent, Jr Exper Med , 1930, lII, 701-716
- ²LONG, P H , DOULL, J A , BOURN, J M , and McCOMB, E The etiology of acute upper respiratory infection (common cold) Jr Exper Med , 1931, lIII, 447-470
- ³VAUGHAN, VICTOR C Epidemiology and public health, 1922, 1, C V Mosby Company, St Louis, 83
- ⁴DOCHEZ, A R , MILLS, K C , and KNEELAND, Y, JR Study of the virus of the common cold and its cultivation in tissue medium, Proc Soc Exper Biol and Med , 1931, xxvIII, 513-516
- ⁵SHIBLEY, G S , HANGAR, F M , and DOCHEZ, A R Studies in common cold I Observations of the normal bacterial flora of nose and throat and variations occurring during colds, Jr Exper Med , 1926, xIIII, 415-431
- ⁶SHIBLEY, G S , MILLS, K C , and DOCHEZ, A R Studies of the etiology of the common cold, Jr Am Med Assoc , 1930, xcV, 1553-1556
- ⁷WALKER, J E Infection of laboratory worker with *Bacillus influenzae*, Jr Infect Dis , 1928, xIIII, 300-305
- ⁸WALKER, J E Production of colds with *Micrococcus catarrhalis*, Jr Infect Dis , 1929, xIv, 254-256
- ⁹SHIBLEY, G S , MILLS, K C , and DOCHEZ, A R Further consideration of transmissibility of human upper respiratory infections (common cold) to the ape, Proc Soc Exper Biol and Med , 1929, xxvII, 59-60
- ¹⁰WALKER, J E A cold caused by *Bacillus bronchisepticus*, Jr Am Med Assoc , 1928, xci, 1108-1109
- ¹¹PARK, W H , and COOPER, G Accidental inoculation of influenza bacilli on the mucous membranes of healthy persons with development of infection in at least one Persistence of type characteristic of bacilli, Jr Immunol , 1921, vI, 81-85
- ¹²CECIL, R L , and STEFFEN, G I Acute respiratory infection in man following inoculation with virulent *Bacillus influenzae*, Jr Infect Dis , 1921, xxvIII, 201
- ¹³VON FENYVESSY, B , and KOPP, H Beiträge zur Aetiologie der Influenza, Centralbl f Bakteriol , 1926, xcviII, 477-484

A Layman Considers Migraine*

By WALTER B. SHEPPARD, *Denver, Colorado*

A LAYMAN, who has been subject to migraine for forty-seven years, who is quite familiar with its voluminous literature, and who is fairly well versed in what little is known about the human metabolism, may possibly have made some observations worthy of notice by the medical fraternity

ETIOLOGY

Migraine is not an ache, but an acute pain, typically localized above and posterior to the supra-orbital process, but it may rarely be parietal or occipital, and it may switch its site in different attacks or in the same attack. It is a distinct pathological entity, always inherited, though in transmission it is not always true to type, and the heredity may thus be obscured. It usually

begins in childhood or adolescence, seldom after 19. The precise nature and basic causation of the disorder are still shrouded in mystery. No explanation fits. Every theory is shattered by some specific incompatible clinical fact. Anything that lowers a patient's threshold of resistance may precipitate a seizure,—may pull the trigger, so to speak,—but what loads the gun is wholly unknown.

While the disorder is incurable, and is prone to increase in severity and frequency, it tends often to remit, in women more or less abruptly at the menopause, and in men to taper off with the gradual subsidence of gonadal activity, but many sufferers find relief in the grave alone. These spontaneous recoveries would seem to impose a complete negative on all attempted etiologies, including the latest candidacy, sensitization.

*Received for publication, February 19, 1932

NOTE BY EDITOR. The author of this paper is now 66 years of age. He believes that he inherited his tendency to migraine from his mother. It first appeared when he was in college at the age of 19. He has been an editor, but so severe and so frequent have been his attacks of migraine that he dare allow himself but two or three hours of close mental application a day. He has read extensively of migraine and has experimented with himself for nearly a half-century. The record of his observations and his conclusions cannot but be of interest and value to professional readers.

There does not appear to be much valid evidence going to show that migraine's relation to allergy is anything but fortuitous or coincidental. Out of 441 perennial hay-fever cases studied by Balyeat, 17 only, or 3.8 per cent, presented the migraine complication, although more than 50 per cent, all told, had some other indisputable allergic reaction, such as asthma, urticaria, or eczema. The fact is, in the early years of migraine, almost any

medical intervention, or improvement in regimen, or removal of some proximate cause, such as dietary indiscretion, eye-strain, constipation, or the like, may effect a "cure", which is not permanent

Possibly the most plausible explanation of the migraine complex, as yet totally unsubstantiated, is to ascribe it to some specific metabolic or endocrine idiosyncrasy. It is apparently not easy to account otherwise for the spontaneous recoveries, which occur, if at all, almost invariably in the last decades of life. That failing gonadal function, or any concomitant of the same, can have any causal relation to anaphylaxis, is a tax on credulity. In common with all forms of life, mankind universally in senescence or sooner becomes sexually impotent. But migraine may persist till the end of life, even to the seventh or the eighth decade. It is in the later decades that resistance to anaphylactic shock should, *a priori*, be at its lowest ebb. In theory, therefore, if allergic in origin, migraine should never be "cured", in the latter end of life. In truth, however, recoveries almost never occur at any other time, while the true allergic disorders evince no disposition to cease at this period.

There would seem to be some color for the suspicion that the spontaneous recoveries are related to a diminishing or suspended supply of some unknown hormone or catalyst, that has, earlier in life, been thrown into the bloodstream in excess, or of faulty quality. This notion is not in conflict with the invariable tendency of all glands, unless it be the prostate, to subinvolute in later years, and with the fact that func-

tional and anatomical abnormalities are prone to be transmitted

PRODROMES IN MIGRAINE

For a day or more before the attack, the patient is likely to be jerky and irritable, his muscles may twitch, especially those of his face and eyelids, and at night he may be awakened by the frequent involuntary contraction of legs and arms, as well as by the itching of his skin about the nose and mouth. Sleep has been broken and unrestful, partaking of the twilight variety, though on the night immediately preceding the attack, it may have been "druggy". While the seizure is brewing, there is apt to be a ravenous appetite, accompanied by a pronounced sensation of tension in the abdominal viscera, together with borborygmus. There has been, the day before the onset, an unusual subjective feeling of complacency and competence. If there was shock, mental or physical, it entailed an excitation, closely resembling that induced by an overdose of caffeine, the patient can not "let down", or stop the pounding of his heart, or make his mind behave, a torrent of thoughts and images pours through his brain for hours,—and the state is apparently objective wholly, due perhaps to some disturbance of the endocrine balance.

The actual onset may begin at any hour, but it most often occurs in the morning, after some stress or imprudence of the day previous. It is often ushered in by a slight dull ache through or above the eyes, at this stage indistinguishable from the mild negligible aches caused by or accompanying constipation, eyestrain, fatigue, hyper-

chlorhydria, scanty ingestion of fluids, and the like

While the day before, the patient felt equal to almost anything, this morning he is lethargic, inert, and equal to almost nothing. He lacks appetite, and his food does not taste right, his vision is changed, and his lenses, if he wears any, do not fit, owing to distortion of the eyeball. Feet and hands are cold and clammy.

The prodromal stage may not be very noticeable, and may last for days before the actual onset, and may even be aborted by purgation, especially early in life, or an attack may be precipitated by some trifle. Or the symptoms may subside without medication. Beginners, whose seizures occur infrequently, can almost always stave off any individual attack by prompt and vigorous catharsis, by a saline or aloin, if exhibited on the first appearance of the characteristic prodromes, which every patient soon learns to distinguish almost unerringly.

SYMPTOMATOLOGY

At the outset, migraine may occur not oftener than once or twice a year, or even less frequently, later as often as twice a week. In truth, in severe types, reckless indiscretions are fully capable of inducing repeated seizures, one after another, so close together as to be practically continuous. Early in life the attack may be slept off, or may end with emesis, later, the duration may be so long as a week or more. When the habit has been fully established, two or three days, in the absence of medical intervention, are about the average. The characteristic pain may be a by-product, for the custom-

ary concomitant metabolic disturbance may endure for days after the pain has ceased.

Scotoma may usher in an attack, but either may be present without the other. Periodicity, except in women at the menses, is not marked. Long-standing cases take no account of periods. Pain and the metabolic explosion may be so severe and prolonged as to induce symptoms of traumatism. Toxemia may be so profound as to resemble uremia in all respects except casts and albumin. Exceptionally heavy visitations may be accompanied by arthritic symptoms in maxillary and neck muscles, on the same side as that on which the pain is localized, and this pseudo-arthritis may last for weeks.

There is often a drop in bodily temperature, even to 95° or less, and a rise in systolic pressure, but neither manifestation is invariable, during attacks. There is nearly always more or less pneumogastric disturbance, as evidenced by dyspnea, arrhythmia, excess secretion of saliva and of nasal mucus. As in gout, there is apt to be polyuria before seizures, but during the attack, the urine, as in gout, is pretty sure to be scanty and heavily charged with solids. Peristalsis is usually diminished before and during the attack, but migraine may occur during diarrhea or catharsis.

The tongue is usually, but may not be, furred; a blackish tinge is an index of the severity of the visitation. During seizure, the temporal arteries may be much distended, while the distal arterioles are constricted, but marked vascular change may be absent. It is possible that the pain may be caused by a vasomotor disturbance in the cerebral

cortex, as has been postulated, but there is no clinical evidence going to establish the validity of this theory and that edema could occur hundreds or thousands of times in the same area, with no resultant structural change, or mental impairment, is hard to believe.

Before the actual onset, there may be marked mental depression, and during, before and after, considerable hebétude. The patient does not lose his zeal, but regardless of pain and malaise, he is able to do very little. His mind refuses to do his bidding, he feels as if drugged, he can not recall names, or remember what he reads or hears, he misuses words, has difficulty even with his wonted daily routine, can not trust himself to compose a business letter, all his sense-perceptions are more or less obfuscated, especially sight, hearing, and taste.

While nausea is common, emesis is often impossible, so that undigested food may remain in the stomach during most or all of the attack. There is probably always hyperchlorhydria, caused perhaps by hepatic congestion, and the excess of acid may abrade the stomach mucosa, so that eructations are streaked with blood. Even if or when emesis is induced, the stomach may continue to "buck" for hours after it is emptied, even water may not be retained. Heart action is usually slowed down, even to 50 per minute, and the radial arteries are usually threadlike. Tenderness of scalp, at the seat of pain, is common, and there may be desquamation at the same site.

Early in life, any individual attack is likely to end abruptly, after vomiting, or purgation, later, remissions are usually gradual, extending over hours

or even a day or more. As a rule, sleep is difficult to compass, during attacks, regardless of pain. Loss of sleep, together with exhaustion from pain, may induce between attacks and during them an added constant headache of neurasthenia. Thus the patient, unless or until he capitulates in some degree, may be reduced to helplessness.

The onset of migraine is usually not sharply defined, most often it travels with a leaden heel. The pain is apt to begin diffusely through the eyeballs, or frontally, over the brows, but it soon localizes, and is justified of its name, hemicrania. With actual advent, the patient's feeling of tension may abate, but this may be partly auto-suggestion, for this pathology inculcates resignation, at least after thirty or forty years of suffering. In that migraine is essentially a toxemia, it is rather odd that it does not seem to shorten life or impair mentality. On the contrary, its victims are not below the average in acumen or longevity. Trudeau told this writer that possession of this complex seemed to inure to the advantage of those with pulmonary tuberculosis. And it is a fact, that any intercurrent infection with pyrexia will result in complete freedom from migraine for weeks or months. But any vicissitude, as prolonged convalescence from severe illness, or traumatism, may be followed by marked and lasting exacerbation of the migraine.

PROPHYLAXIS IN MIGRAINE

In that migraine is incurable, intervention would seem especially indicated along the lines of prophylaxis. Anatomical abnormalities impairing function should be removed, defective vision

aided with proper lenses, practices that lower body tone discarded. But after all has been done, the patient still has his migraine. At most, the sphere of his activity may have been widened somewhat for a time. But, as he is usually ambitious and unable to achieve a vegetable existence, he is apt to transcend his limitations as much as before, so that the net result, so far as the migraine is concerned, is pretty sure to be nearly nil.

It is not possible to devise a regimen for every individual case. Prophylactic expedients are many and varied, and should include. A maximum allowance of sleep, a minimum of stress, mental or physical, a diet carefully regulated, both as to quantity, quality, and components, an active elimination.

Migraine being a toxemia, its victims have much to oxidize. By reason of over-acting adrenals, hepatic and thyroid efficiency is constantly impaired, and peristalsis slowed down, while pancreatic activity is diminished. That is, metabolic instability is accentuated at the very time that elimination is subnormal. Apparently the chief function of sleep is to enable the body to clean house. Hence these patients need all the sleep they can get. Even twelve hours per diem, including an afternoon nap, is none too much in long-standing cases, if patients can get it. Few can attain this maximum, as the toxins in their bloodstream irritate the higher nerve centers and make them sensitive to objective impressions during sleep. Quiet sleeping places are not easy to come at now.

Emotion is the great proximate precipitant, and the migrainous appear all to be of unstable equilibrium. Even the

ordinary wear and tear of daily routine are trying to the typical patient, and to shield himself is all but impossible. For, after his family circle or business associates have witnessed scores or hundreds of seizures, they inevitably become callous, and his sufferings come to be regarded as partaking of the nature of hypochondria, or malingering. And this reaction acts as a spur to the patient himself, to his own undoing.

An outdoor, carefree life is the ideal, but few can arrange it. Excitement, especially sex, cards, social whirl, movies, overwork, tension, worry,—all have their price. A business or professional man may be compelled to retire, but a mother can scarcely abdicate, and for her, romping children, or a wayward adolescent, or a cocky servant, or cheating tradesmen may be as inimical as almost any factor imaginable.

Most people eat too much. Excess is normally burned up by the liver and thyroids. But the oxidizing capacity of the migrainous is already overtaxed. Hence, their intake should by experiment, be reduced to a minimum, which for those not engaged in manual labor, should probably not exceed 2,000 calories per diem. Animal proteids should be used sparingly, for when improperly converted into amino-acids by trypsin, they are decidedly toxic, and in the migrainous, pancreatic function is seldom perfect. And on this account, meat is best handled when comminuted, as in Hamburg steak.

The purin-producers, such as coffee, alcohol, tea, chocolate, should be abjured, for purins are hard to eliminate, and appear also to be specifically irri-

tating to the nerve centers The customary heavy meat meal at night should be abandoned, because it is then that the metabolism is at lowest ebb

A neutral blood plasma promotes elimination, and it is a biological commonplace that cell activity goes on best in a neutral medium Neutrality is promoted by the liberal ingestion, daily, of vegetable juices, most easily achieved by boiling the vegetables and drinking the pot-liquor Stewed fruits, if sub-acid, are also excellent Citric and malic acids are justly under suspicion Nearly all these patients suffer more or less from spastic constipation, and cellulose in large quantity tends to plug up the alimentary canal, hence the suggestion that needful vegetable juices be obtained by boiling, rather than by direct consumption of the fiber Cellulose, also, is broken down by bacterial action in the colon, a process productive of gas, irritating to both sympathetic and vagus, which are undoubtedly concerned actively in the migraine complex

Unless contra-indicated by vascular or cardiac or renal pathology, every patient should drink at least two quarts of liquid per day, it is expedient to complete this by 4 p. m., as a full bladder interferes with sleep Many or most subjects do not tolerate casein, milk, therefore, is not for such Any excess of sugar is stored in the liver in the form of glycogen, and this storage and oxidation are incompatibles, hence the wisdom of using sugar very sparingly Fats are also not well borne Ben Jonson, in "Volpone", written in 1605, remarked the fact that the Dutch, much addicted to balls of butter, had to purge after such indulgence The

relative inability of the migrainous to handle fats well seems to be specific Gas-formers, such as the legumes, cabbage, oatmeal, spices and condiments, should be left severely alone Food purveyors are now pretty sophisticated Artificial preservatives, such as sulphur dioxide, and coal-tar flavoring extracts and colorings, are in extremely common use, and as a whole they are excessively deleterious to the migraine subject Unless or until all such are eliminated from his dietary, little or nothing can be accomplished for his relief To fend against them is almost impossible The preservatives are common in cured meats and fish as well as fresh, evaporated fruits, molasses and syrups, milk and cream, etc., and the coal-tar derivatives are in high favor with bakers and candy-makers

Empirically, a varied diet is best Apparently in all these patients, pancreatic enzymes are sometimes if not always lacking in quantity or quality, and trypsin can not break down starch, nor can lipase, proteids, nor diastase, fats Starchy foods must of necessity be the mainstay, and bread and butter with fruit or vegetable juices furnish very nearly a balanced ration Bread is the sole food that a civilized palate can endure at every meal, and it alone has been subjected to a temperature so high as 500° for so long a period as one hour, thus insuring the breaking down of the starch granules Personal idiosyncrasies in diet are mostly imaginary, though allergy is an undoubted fact Every patient should, by careful experiment, work out a menu for himself and adhere to it so far as possible But not every layman is competent to do this, and even dieticians are apt to

conclude, if shellfish or strawberries provoke in their own persons urticaria or the like, that such foods are unfit for human consumption. And migraine patients are especially given to ascribing, wrongfully, a given visitation to some viand previously ingested. Any food, taken in moderation, has in all likelihood, an extremely faint causal relation to any individual attack of migraine, albeit a pronounced allergic reaction might conceivably, like any other factor contributing to the lowering of the threshold of resistance, become the proximate precipitating cause of trouble. Generally speaking, gastronomic joys should be mostly tabu to severe types of migraine. In fact, the average subject would reduce his sufferings almost to the vanishing point, if only he could subsist without eating at all.

MEDICATION IN MIGRAINE

In the way of medication, the two sheet-anchors are cannabis indica (Herring's) and calomel. Cannabis is fool-proof, to all but the fools to whom bread-pills are habit-forming. It alleviates the pain during seizures, and by obtunding the sense perceptions slightly, it interposes a barrier or curtain between the patient and the slings and arrows of outrageous fortune, which imperviousness increases with use. And it does not check the secretions to any appreciable degree. Some patients are entirely relieved by cannabis as long as it is exhibited. Initial dosage should not exceed $1/12$ grain, repeated three or four times each day. The maximum objective is $1/4$ grain every four hours while awake. During stress, this maximum may be usefully

exceeded. Every migraine subject, unless abnormally susceptible to auto-suggestion, should be put through a course of this drug, it is the nearest approach to a specific.

To abort or break up any given seizure, nothing takes the place of calomel. Its handling is an art, which each patient must to some extent acquire for himself. For no two patients are precisely alike, nor are any two visitations identical in the same individual. Calomel is not altogether foolproof. It usually gives such relief, that there is a temptation to abuse it, it is hardly adapted to daily use, if for no other reason than that it must be excreted through the kidneys.

Upon the first prodromal symptom, which the patient can almost unerringly detect, he should take probably not less than $1\frac{1}{2}$ grains, though some patients may require more, to abort the impending attack. If this does not result, after 12 to 18 hours in relief, the initial dose should be repeated. If the pain persists, after another 12 hours or so, the sufferer should take his full maximum, which may be anything up to six grains or so. There is no sense in allowing the agony to continue for days. The total amount required bears very close relation to the degree to which the patient has flouted his limitations, previous to the onset.

Calomel in small doses is decidedly not indicated; for the disorder and concomitant metabolic explosion travel so rapidly that repeated tenth-grains can not overtake the procession of events. And after the complex has been permitted to attain its climax, it may be days before the pain can be stopped, and much longer before the

metabolic equilibrium can be restored Epsom salts, on an empty stomach, in plenty of water, should usually follow, after the pain has ended, albeit the salts may not be necessary, if the patient is taking a daily laxative For those patients who can not tolerate calomel, podophyllin, in 1/4 or 1/2 grain doses, taken in plenty of water, may answer as an *imperfect makeshift*

Every patient should induce, at least experimentally, not less than two loose evacuations daily Catharsis, by inaugurating profuse watery discharge from the rectum and sigmoid, undoubtedly carries off much toxic material and thus lightens the liver's load Aloin is the ideal laxative, and it alone may hold the lid on migraine for years, it can be exhibited for a lifetime with little or no ill effects discernible Anyhow, it is a condition, not a theory, that confronts these patients Addiction to laxatives may have drawbacks, but as a choice of evils, migraine is the greater Salines and enemata are not for prolonged use

After a siege, migraine patients

might well avoid violent exertion Pain weakens the heart-muscle, and if it is repeatedly overtaxed, the weakness may become permanent Imperfectly acting hearts are not uncommon in these subjects, and such may accentuate the complex Those who have chest-pains, extra systoles, arrhythmia, or chronic digestive disturbances might profit by a *course of digitalis*

The migraine subject of pronounced type is among the most miserable beings on earth, for the sum total of his sufferings, mental as well as physical, probably surpasses that which ordinarily falls to the lot of several hundred normal persons throughout their mundane existence Genius has been defined as the capacity for infinite pains-taking Without this faculty, to combat a lifelong migraine, is a task to tax the patience of a saint, and the courage of a paladin Mankind, however, as Osler justly remarked, has never emerged from the thaumaturgic age, and most migraine victims want to be cured by taking a pill

Presidential Address

American College of Physicians*

By S MARX WHITE, B S , M D , F A C P , *Minneapolis, Minnesota*

SELECTION by you as president for a year has allowed me to follow in the footsteps of men notable in medicine in this country. For the opportunity I am grateful. The honor brings with it great responsibilities.

This is the second meeting for which the president has been given the responsibility for the program of the General Sessions. This change was made two years ago in the belief that the president, using the prestige of his office, would have a more ready response from invited guests, domestic or foreign, and would have the opportunity to use speakers of his own choice rather than to select material voluntarily offered. The excellent program for the General Sessions presented by President Miller at Baltimore a year ago proved the wisdom of the change. This year, in spite of unusual difficulties, a program representative of the progressive spirit and of the latest advances in medicine is presented.

During the year which has elapsed since the Baltimore Session, the College has lost by death one Master,

twenty-five Fellows and six Associates. It is customary to publish in the *ANNALS OF INTERNAL MEDICINE* a biographic sketch of each, but some losses, because of their significance to the College, deserve special mention.

Dr Reynold Webb Wilcox of Princeton, New Jersey, died June 6, 1931, at the age of seventy-five years. He was a long time Professor of Medicine at the New York Post Graduate Medical School and Hospital, the author of many articles in American medical journals and of a well-known work on *Materia Medica and Therapeutics* which ran into ten editions. He was largely instrumental in the organization of the College, was a charter member and after the College had secured its charter on May 11, 1915, under the laws of the State of Delaware, he became the first president, continuing in that office until 1922, relinquishing it then to Dr James M Anders of Philadelphia, but maintaining an active personal interest in the College.

Dr George Martin Kober, born in Hesse Darmstadt, Germany, lived to the ripe age of eighty-one years and served his adopted country with distinction. In the last decade of the nineteenth century he directed attention to the pollution of the Potomac

*Delivered at the San Francisco Session of the American College of Physicians, April 6, 1932

River water as a factor in the spread of typhoid fever in the National Capitol, his home city, and was the first to point out also the part played by flies as carriers of the disease. His activities helped greatly to secure the legislation and appropriations by Congress necessary for proper sanitation in Washington. He remained active and interested in medical affairs until the very end of his career and the charm of his personality contributed much to the interest of medical meetings in which he was an attendant or participant in discussion.

The career of Dr Francis Xavier Dercum, world famous neurologist, closed suddenly and unexpectedly at the age of seventy-four years as he, then president of the American Philosophical Society, sat in the chair formerly occupied by Benjamin Franklin, and was about to open the 204th annual meeting. "He died", remarked a fellow scientist, "as a scientist would wish".

Dr Leonard M. Murray of Toronto was elected to the Board of Regents of the College in 1923 and served the two terms of three years each allowed by the by-laws. His contributions to our knowledge of cardiovascular disease are well known. He was only fifty-six when he passed away suddenly and unexpectedly in the midst of his career and left the memory of a charming personality and warm friendliness with those who were privileged to come in contact with him.

The death of Dr Aldred Scott Warthin, a Master of the College, at the age of sixty-four closed a remarkable and brilliant career while still in full tide. No single individual has

made so great a contribution to the welfare and development of the College and the ANNALS OF INTERNAL MEDICINE as he. Appointed editor in 1924 he brought the ANNALS to a most authoritative position in the medical literature of this country. The first four years spent by him in teaching at the University of Michigan, from 1891 to 1895, were in internal medicine under Dr George Dock. This colored his thought in later years, for no pathologist of his time thought with and for clinical medicine more assiduously or effectively than he. This attitude rendered him particularly useful and acceptable as editor of the ANNALS. He understood and labored for the interests of clinical medicine. During the last year of his life he occupied himself particularly in the aims of the College. He felt that the College was just entering its greatest period of usefulness. Shortly after the Baltimore Session, and a few hours before his death, which came unexpectedly, he dictated a long letter to me, charged as I was with the responsibility for the program of this present session. In this letter he said, in part "I think that I would like to be on the program next year at the California meeting. So many men have written to me concerning various matters pertaining to the College that I would like to make an address bearing upon the future of the College and its functions. The editorial which I had in the number preceding the meeting of the College apparently excited a good deal of thought and I am glad to see that there is a growing appreciation that the College should sometime have something more than mere scientific work.

I think that there is a real opportunity to make the College a more vital force and influence in American Medicine than it is at the present time" The letter is unsigned but was forwarded to me immediately after his demise and breathed the spirit of the man. What the concrete suggestions were we know only in part. He had never formulated them completely to anyone, so far as is known. Their spirit, however, was one of a positive attack on the problems—cultural, professional and economic—facing at least that portion of the medical profession represented by the College. They were the outgrowth of a rich experience and a trained and cultured mind. No quotation from this editorial, detaching a part from the whole, would adequately represent his thought. Rather would I refer you to its entirety in the *ANNALS* for February, 1931.

It is a source of personal gratification to be able to pay tribute to the man who has carried these many months the work so abruptly relinquished by Dr. Warthin. At a sacrifice of time needed for other interests, Dr. Carl V. Weller, Professor of Pathology at the University of Michigan, has edited the *ANNALS OF INTERNAL MEDICINE* in a manner beyond criticism. The editorial writing has been carried on with eminent satisfaction to all, welcome changes and improvements have been made and the rapid growth in size, character and influence, well under way during Dr. Warthin's lifetime, has continued without interruption. To him we express our profound gratitude for this loyal and effective service.

The growth of the College contin-

ues without interruption. The mechanism by which a period as an associate is a prerequisite for fellowship, became operative with the close of the year 1931. Time alone will demonstrate whether this change will accomplish its purpose. While the College has not as yet become unwieldy because of size, it was apparent that such a time was approaching and that it was desirable to prevent, in a healthy and logical manner, too rapid expansion. The period of time required as an associate will give the College an opportunity to appraise the spirit and accomplishments of each candidate for fellowship, and will give the candidate an opportunity to learn more fully the purposes and service fundamental to the success of the College. The new plan makes it mandatory that each candidate for associateship be scanned with as great care as that formerly used in selecting nominees for fellowship.

I call the attention of the Fellows of the College again to the opportunity presented in life membership. While economic conditions during the past two years and more have slowed accession in this department, those in position to do so have an opportunity even greater than before. Moneys derived from life memberships are set aside in a separate endowment fund, through which the scientific aims of the College will be advanced. The College will attain that influence and power at which we aim only when its resources are adequate to accomplish its purposes. The endowment fund may receive accessions in many ways. Life membership should be purchased not by the few, but by the many. Let us be reminded that the initiation fee is a credit already

paid toward the cost of life membership. The number, instead of about thirty, should be three hundred and more. Donations, small when necessary but generous if possible, should be a habit and not a rarity. Arrangements for bequests at the death of members or of others interested in medicine should be discussed and encouraged by us. To those of us unable to purchase life membership, I would suggest a bequest of an equal sum *In Memoriam*. Philanthropically minded friends and clients should be told of the opportunity for continued usefulness of their moneys under skillful direction by the Board of Regents which is a continuing body of men wise in the use of funds for the advancement of medicine. Such funds as donations or bequests to the College are free from gift or inheritance taxes, an inducement to many at a time when taxes of all kinds are becoming a burden. Such matters as these should become subjects of free conversation with us, for the philanthropist often keeps his purposes in hiding and his gifts may be revealed only by his testament. We have made a beginning, \$52,400 since 1926. This should give us courage, but it is too slow. We would each like to see the fund in effective operation during our lifetime. With enthusiasm and interest on the part of our entire membership, or of only a significant portion of it, I am confident that many sources not yet uncovered could be found for the endowment fund. Additions of any kind, many and small, fewer and large, would swell it to a place of real power and usefulness.

As a new departure, an example of activity outside of the primarily ex-

pressed purposes of the College, we have had this evening the presentation of the John Phillips Memorial Prize given annually by the College in memory of that beloved physician, who gave his life in so tragic a manner that others might be saved. A member of the Board of Regents from 1923 until the time of his death in 1929, he served the cause of Medicine and the College with distinction. It is fitting that his life and work should be brought again to mind through the presentation of the prize and by an address by Dr. Oswald T. Avery, the distinguished first recipient thereof.

Our progress depends upon the devotion, the intelligence and the continued application of the coterie of men devoting their lives to the advancement of knowledge. The direct financial rewards for research in medicine and in other branches of science are pitifully meager and the workers are often seriously handicapped by lack of the support needed in their pursuits. To this group of men every honor is due and by them every financial aid is used to further their research. The very fact of devotion to their calling is an evidence of their earnestness of purpose. Every aid rendered them brings its return many fold. The College is in the forefront in its encouragement of scientific work. Money is needed in order to further this and similar enterprises. The endowment fund, aided by life memberships, will exercise a most potent influence in this direction.

The past year has seen cancellation of many medical meetings and Congresses planned in Europe. There the change in economic status has reached into every phase of life and this

restricted activity has thus affected the time given to consideration of the most fundamental human needs, of health and physical welfare. To the west of us Japan and China, profiting nothing by the horrid experiences of newer civilizations, have been employing the age-old methods of Martian struggle, and medicine there is compelled to occupy itself with binding up wounds, removing the sick and injured from the lines of communication and, in so far as possible, restoring them to their destructive occupations. In the meantime, progress in constructive medical thought and effort is halted. In this continent we are blessed with a common language and understanding. The long boundary between Canada and the United States needs no military fortification or patrol. We have a common inheritance and understanding and for long have been able to adjust any differences of opinion by peaceful means. We can thus continue our constructive efforts. With our neighbors on the south, although handicapped by differences in language, we are at peace and will so remain. Our common interests have taught us to avoid destructive means of settling questions between nations. Our situation, therefore, calls for increased effort in the arts of peace.

When discussing the functions of the College we should be reminded of our duties and privileges in the American Medical Association, since all forms of activity of those licensed to practice medicine are there represented. To it we individually and collectively give our allegiance and support. Its great medical *Journal* and *Hygeia* lead in their respective fields of general

medicine and surgery and of popular hygiene. Two of the major activities of this association are of such significance to medicine that they deserve particular mention, not only for themselves but as examples of what collective efforts in a great association may accomplish. The first of these is that of the Council on Pharmacy and Chemistry. This Council has done, and is doing, a service of incalculable value to the medical profession in freeing us from the need of reliance on secret and proprietary preparations and has given us standards by which all remedies may be judged. Not only as individuals but as an organization there should be specific and expressed approval of the work of this Council and an active adherence to the principles it has laid down. Only by strict compliance with its requirements can we hope to keep therapeutics on the high plane it should occupy, free from all secret remedies and with positive knowledge, openly arrived at, of the character of all therapeutic procedures.

The second major activity in the American Medical Association to which our support is due is that of the Council on Medical Education and Hospitals. The association, together with the forces and organizations whose support it has enlisted, has been a major factor in placing medical education on the high plane it now occupies in most states. The elimination, now almost complete, of the low standard commercial medical schools and the establishment of standards more nearly uniform throughout the country has been a service of prime importance. In the matter of hospitals the activities of the Association has been limited largely

to the educational aspect, the training of internes, and the opportunities for special training for residents. The important function of standardization of hospitals was assumed by the American College of Surgeons while the Association slept, and before our own organization, to represent medicine as that college represents surgery, was developed. All credit is due that college for its enterprise and for the energy with which its standardization project is carried out, but the anomaly of surgeons posing the standards for the physician is apparent to anyone who has the welfare of the whole profession, and of the patient as well, in mind. It is probable that only the assumption of greater responsibility by the American Medical Association will help to correct this unbalanced state of affairs. Renewed attempt to further the interests of medical service in standardized hospitals may yet avail. In spite of this disadvantaged position of internal medicine at the present time, the public is acquiring a growing appreciation of the part to be played by hospitals in diagnostic and medical forms of service. While it is, undoubtedly, true that in many hospitals surgical service is the chief aim, it is equally true that the growing complexity of equipment necessary for adequate medical service is forcing the patient with non-surgical disorders into the hospital where the proper equipment can be provided and more effective study made.

Is it possible that there is a distinction between the medical and surgical interests of a patient? I cannot agree that there is. The interest of the patient demands, except in emergencies and with the diagnosis readily made, a

thorough survey to discover first of all the character and the sum of conditions and disorders present and, secondly, not primarily, the therapeutic procedures to be applied. The degree of skill and experience necessary for the solution of a diagnostic problem is just as great as for the performance of an operation. There has been a tendency to foster the idea that long training and special experience are necessary to make a surgeon, but that anybody can make a diagnosis, or can carry out medical lines of therapy with tolerable accuracy. In fact, during the last two years, particularly, it has been a source of some amusement, if not pain, to see some of our erstwhile surgical confreres indulging in the mysteries of digitalis, the diuretics and some of the rest of our wellworn armamentarium in the intervals between their now all too infrequent operations. At some time in the near future it may be necessary for some organization, either this or the American Medical Association, to insist upon an adequate recognition of medical, as well as of surgical, values in hospital service. It is to be hoped that the invitation to that end may be given by the organization which has so far kept that function to itself. By this means a service of greater value, both to the medical and surgical interests of the patient, could be performed.

The primary purposes of the College are well set forth in our constitution. There has been much discussion as to additional activities a body such as this might well undertake. To the present it has been thought advisable to concentrate on making the foundation sound and sure, and on assuring a

membership representative and inclusive of the men in the United States and Canada best fitted by character and training to understand the problems of our special fields. Standards of character and attainment have been set but there has been no thought of limitation in numbers. As a result of this policy the College has attained in the sixteen years of its existence a position of influence in internal medicine. The annual session has been the outstanding and most valuable meeting of the year. The clinics and demonstrations at the place of meeting by the men of the schools and hospitals have given those attending the session an insight into the character and breadth of the medical work in each of the great cities visited, thus giving an opportunity to each Fellow to compare the work in his own locality with that in widely scattered medical centers throughout the country. This in itself is one of the most valuable features of our sessions.

At this point I should like to call your attention to the extraordinary depth and breadth of the clinical program arranged here in San Francisco, and to thank, for the College, Dr Wm J Kerr, who has filled with distinction the position of General Chairman.

With the cultural background of the Fellows of the College it is natural that the history of medicine should receive considerable attention and should have at least some place in our program. In this, and the two sessions preceding, we have given it more attention than in previous years and have sensed a favorable response on the part of the membership. This year we find this stimulating and wholly enjoyable ac-

tivity of many of our Fellows exemplified not only in the general sessions, but also in the series of exhibits and papers on medical history in the clinical sessions. Historical considerations, however, can claim only a minor portion of our time and other organizations among medical men are giving it more serious attention. To them we extend every aid and encouragement.

We glory in our past, not only remote, but so immediate that it may be called the present. The achievements of medical science need no catalogue here. The conquests of infectious and other forms of preventable disease, the consequent prolongation of life, the prompt application of all forms of scientific discovery to our problems as we have cast off the cloak of mystery once worn, have all placed medicine in the forefront of this progressive age. Our scientific problems loom large, but are being attacked by the best minds on every hand. The serious difficulties confronting us as a profession today lie as much in the social as in the scientific field.

Broad and vexing questions in what may be called the field of medical economics are constantly arising. Their solution needs wise and unselfish leadership. The medical profession is taking what is believed to be its proper part in the five year study of the Committee on the Costs of Medical Care. Some results of these studies have appeared from time to time and the five years allotted will have elapsed at a relatively early date. Some definite recommendations will be made. It is hoped that some new applications of our age-old principles will be suggested and that some new, or so far relatively

untried, methods of organization will receive attention and may be recommended, at least for trial. That the committee can solve, even within a five year period, all of even the major questions posed is not within the bounds of human possibility.

The existence of the committee has made the public more acutely aware of our economic shortcomings than of our virtues, and whether we wish it or no, forces not of our own choosing will attempt to invade what we believe to be properly our domain. The paramount interest is that of the public. Public interests are often expressed in the form of legislation, but legislative bodies are notoriously lacking in an appreciation of medical values and it is only when guided, or driven, by an aroused medical opinion that legislation actually in the public interest has been secured. One doubts legislative wisdom in the medical field, or for that matter in any other field where science is involved. One needs only to cite the legislation involving cults in most of our states for illustration.

Dr Ray Lyman Wilbur, writing as Chairman of the Committee on the Costs of Medical Care, states pointedly that the achievements of medical science must be made available to all, that the only way this can be done is through organization, that the organization of medical facilities will be painful to some even if necessary, and that we must make many shifts and changes in our thinking if adequate medical services are to be made available at reasonable cost to the citizens of this country. Two questions arise. What shall be the forms of those organizations? Shall they be determined by states or

communities, or shall they be by medical men themselves?

The various ways in which organization may affect medical service as it relates to disease and disability, i. e., to the practice of medicine, may be thought of as in four great groups.

1. The state and other political units which already provide for certain medical needs of the public. Among these is custodial care of the insane and the incompetent. There is provision for isolation of those whose infectious disease would otherwise be spread throughout the community. There is the study and control of public health relations, and there is, finally, medical service in all its forms for the indigent. In all these ways the state, through organization, can provide service better than the individual. Many people affected by these services could pay for them if necessary, but with the public needs paramount it is clear that the state can perform the service with the welfare of the state in mind. It is only when the state proposes to serve in other ways the individual who is able and desires to pay for individual medical service that we take notice. In the medical mind, the extension of state medicine beyond the needs of police power, public health and public service is inadvisable, largely because of the knowledge that it will do away with the valuable personal relation between physician and patient, necessary if the interests of the patient are to remain primary.

2. Lay organizations, lodges, benefit associations and the like have grown in this country, and in many instances continue to grow in spite of the opposition of the medical profession in the

locality In a few instances only have they succeeded in maintaining the high level of professional attainment we seek to guard In these organizations the continued employment of medical men is subject to many considerations other than their ability to deliver an adequate service Insurance companies, either in relation to such activities as life, health and accident insurance, or as a new project of hospital or sickness insurance, or a combination of both, are becoming interested Probably because there is no firm actuarial basis for premiums, and because the past experience in disability benefit is unfavorable, the old line life insurance companies seem to be reluctant to enter this field The work of the accident insurance companies is principally in the protection of their policy holders and we may expect no constructive efforts from that source In all these fields the primary control is lay, rather than medical The medical man is the employee and not the principal In all these organizations, the cost is met by prepayment of a fixed charge, which, though it may be varied somewhat from time to time as the result of experience, is nevertheless relatively stabilized

3 Hospitals are more and more providing centers about which medical men may group themselves The inter-relations of the members of the staff are often only those of proximity, but more and more close ties of interest are being formed with the hospital as a center It seems quite probable that valuable development along these lines can be fostered and that common interests, with more or less definite co-ordination, can be built in and around

these institutions In teaching hospitals a staff of salaried whole-time men, teaching and practicing the various specialties and covering the entire field, is practicing group medicine When in a state owned public hospital with such a staff the number of individuals treated is not limited by the needs of material for teaching, then the institution is furnishing a form of state medicine An interesting form of group medicine often closely related to teaching hospitals is seen in the Student Health services in many of our large colleges and universities

4 Physicians are organizing in many and various ways to manage their own affairs as they relate to the practice of their profession In some instances such organization involves only a combination of facilities in hospitals, or in more or less loose aggregation, for the purpose of securing laboratory and technical service The formation of more closely knit groups in private clinics has been a development in recent years In such groups, either related to or separate from hospitals, the personal relation between physician and patient will be maintained These groups are formed primarily for the purpose of providing every needed facility for fact finding and for closer integration of the work of one specialty with another In a properly constituted group each man may be said to have a dual function The first is as a specialist in his chosen field, the second is as a general practitioner guiding and conserving the interests of his particular patients Specialism in a group becomes less hard and fast than when a man is practicing alone and the specialist in a well constituted group be-

comes more of a general practitioner than he ever would practicing his specialty alone. Group medicine will be in favor with the physician only when he realizes that he can be a part of it, and that his facilities can be thus enormously increased in a manner using each to its capacity. Without some such mechanism the physician cannot own and control his laboratories and his apparatus without an undue and often depressing financial burden. The group in its ideal form represents an expansion of the partnership principle, and allows a community of interest among medical men obtained in no other way.

In a recent discussion of some economic considerations influencing the future of the practice of medicine, at the Annual Congress on Medical Education, Medical Licensure and Hospitals held in Chicago in February, Hugh Cabot, in addition to considering the various groupings possible in medicine much as in the forms outlined above, made the suggestion that "big business" could make a valuable contribution to the forms of medical service. We will grant at once that the dollars made in big business can be put to work for human welfare in forms of medical service. This has been abundantly demonstrated through the many bequests already made, and through the great foundations now in operation. That the methods of accumulating those dollars could well be used in medicine seems impossible. The ideals and practices of big business and of medicine are in many ways diametrically opposed. If by big business there is any implication that a corporation could practice medicine as a corporation, it is to be hoped that question

is already settled in the negative. Business advertises itself by headlines with an eye to selling the product. Medicine *desires* to advertise itself only by the character of its service and results. When medicine advertises for sale that which the great bulk of the public wants, which is a cure and a cure only, it is open to a conviction of misrepresentation. The cure cannot be guaranteed. In the mind of the public, as well as in the mind of the medical profession, big business does not represent the ideals for which medicine should stand. The dominating influence should be that of service and not that of the financial return.

Speaking broadly, the economic principles underlying the provision of medical service will be determined either by the medical profession or by politicians. In the past we have been most influential in determining our qualifications and in setting high standards for ourselves, but having accomplished this, pressure from without—political pressure if you will—has left us woefully surrounded with a fringe of inadequately prepared cultists, whose chief claim to following lies in hasty and correspondingly faulty methods of approach to the problems of the sick and disabled. The cults and quacks rely upon salesmanship rather than service to secure their following. We have been content to rely upon service and are probably, as a whole, the worst salesmen in the world. I would not put salesmanship above service. To do so would be to lower ourselves to the level we decry. It is true, however, that too large a portion of the public fails entirely to understand our attitude and is too little aware of the solid foundation

on which the science of medicine rests. We are forced to recognize the fact that we have not adequately presented our point of view, or the real significance of our service to the public as a whole. This presentation cannot be made and controlled by individuals, for when so done personal interests creep in and the interests of the profession, as of the public, are likely to become secondary. The task of an adequate presentation can be performed only by and through the organized bodies representing medical opinion freed from individual concerns.

In England and Germany the imposition by legal enactment of certain intolerable and debasing conditions has been due in largest part to the refusal or failure on the part of the medical profession in these countries, to meet in adequate form the fundamental medical needs of the peoples involved, or at least to show clearly where these needs are met. Whether or no legislative enactment of similar character lies before us we do not know. Since with us medical legislation lodges, for the most part, with each of the forty-eight states in the Union it is not probable that there will be any attempt at countrywide legislation of a similar character. We are confronted today, however, with the prospect of an enormous expansion of state medicine and hospitalization by those seeking government relief of non-service disability in Veterans' Hospitals and Bureaus. This project is being fostered politically in spite of the fact that the number of hospital beds now available in the country is adequate for the needs and that there are at hand methods of securing adequate medical service for the

veterans, other than by the provision of new hospital beds. These methods would meet the needs, would provide better service without removing the individual from his immediate locality—an expensive and disruptive procedure—and at the same time would avoid an enormous addition to the already over-weighted tax burden.

It may be that we are fortunate in this country in the fact that medical legislation lodges with the States and this fact may minimize the tendency to crank legislation since the questions involved are brought more nearly home to the people concerned. Further, an experiment in medical economics shown to be impractical in one state can be avoided by others.

In studying the needs of our profession, it is well to bear in mind that we exist primarily not for our own welfare, but to provide a certain service to the public. The public interests are paramount and come before our own. In the statement of principles of medical ethics they are declared to be primarily for the good of the public and we should bear in mind in every consideration that only in the degree that we serve the public needs can we hope for, or receive, public approval. In planning our relations to the public, however, there is a question to which I should like to invite your attention. It is this: Who is best fitted to understand the needs of the public when considering the forms of medical service? Is it the physician as representative of the medical profession, or is it the politician as a representative of the public, where, after all, final action will be lodged. Occupied as we are with better things, we are too prone to

believe that our point of view from its own weight and rectitude will prevail. The man, or the profession, that relies alone on these essential features to advance his cause, is doomed to disappointment. *For success in the economics of medicine, as well as in the science and art, the master word is work.*

It seems clear that if we, as a profession, can command effective leadership and exhibit wisdom and capacity, we can continue to provide in adequate form and with proper costs the needed service. This will require constructive statesmanship and unending effort. By these means the danger of political control, of debasing conditions and of state medicine can be greatly minimized, and if they are avoided, it will be by these means alone.

The American College of Physicians will continue to stress the importance of adequate training as preparation for service in medicine. It will continue to put character in the forefront of requirements of the physician. Medical science will be served and every effort will be made to encourage those who, without thought of self, labor unceasingly in the laboratories and in the wards that the boundaries of knowledge may be extended.

The study of the history of medicine will be encouraged and the cultural value of a knowledge of our past will receive recognition. Knowledge, and the power that knowledge gives, will be fostered at every opportunity. These aims have become a part of the things for which the College is known to stand.

Is it time that the College should move out from this more delightful

realm into a consideration of fields not only cultural but economic? If we were living only so long ago as the date of our charter we could, with perfect equanimity and justification, limit our deliberations to the quieter and more enjoyable features of our profession. It would be a joy to step into the study, the laboratory or the ward and to let our considerations be confined within those walls. If we could be sure that the walls would continue to shelter us this might be a safe procedure. It would certainly be the most delightful life to most of us.

Sixteen years, however, have led us into an era of changes in the economic structure more rapid than we yet realize. Like all life, medicine is not static but is dynamic. Its dynamic power, however, is only what we, collectively and individually, make it. With an active and virile membership reaching into every corner of the land it is necessary that we give consideration, not only to our science, our culture and our comfort, but that we take an active part in the changes in the economic structures on which we stand. Our part can best be the encouragement of the method of science, the processes of trial and error in fitting the service of medicine to the needs of the community. Medical knowledge has been won by long and arduous application. The road by which we can arrive at an equal understanding of the economic values in medicine is equally long. There can be no loitering if we are to continue to lead. There is much to learn along the way and it is only by entering the path that we can expect to follow it.

Editorials

THE SAN FRANCISCO SESSION OF THE AMERICAN COLLEGE OF PHYSICIANS

As the special train of the American College of Physicians made its way westward, gathering small increments at various junction points but with its total passenger list not exceeding seventy-five persons, the statement was frequently heard that it was exceedingly unfortunate that for this year of all years a far-western city had been chosen as the place of meeting of the College. Pessimistic prophecies were voiced as to a probable failure of attendance for it seemed very evident that Fellows from the Middle West as well as from the East were finding it impossible to make the journey. The postponement of various European congresses was mentioned frequently as indicating the difficulties facing such organized endeavors. Yet when San Francisco was reached and there was opportunity to circulate among the gathering throng it was evident that pessimism was ill-founded. This became a certainty when at session after session of the general meetings the Ballroom of the Palace Hotel was found to be filled to capacity. Official figures of the registration at the Sixteenth Annual (San Francisco) Clinical Session are now available. The total attendance was 1,585, consisting of 132 visiting ladies, 107 exhibitors and 1,346 members and guests. It is

true that the attendance was largely contributed to by those resident in the Pacific States, who furthered the success of the undertaking by their commendable zeal and loyalty. Yet the wide geographical distribution of those registering was a source of surprise and of gratification. The only states not represented in the attendance were Alabama, Arkansas, Georgia, New Hampshire, Rhode Island, South Carolina, Virginia, and Wyoming. China, Hawaii, and Panama were each represented by a single registrant. In order of numbers attending from each state, California was first, Oregon, second; Washington, third; Minnesota, fourth, Pennsylvania, fifth, and New York, sixth.

The General Sessions have established an impression, which has been voiced by many, that taken collectively they constitute the outstanding annual event in Internal Medicine in this country. The San Francisco Meeting went far to confirm this feeling. The wealth of material, the general excellence of presentation, and the skillful grouping of related subjects all showed the wisdom with which the program was organized. The sustained attendance throughout meetings which were rather too long, and too hurried, showed that the General Sessions were appreciated.

The richness of the clinical material which San Francisco and the neighboring communities set before their visitors must be mentioned also. Mem-

bers and guests were in a more or less constant state of mental unrest in endeavoring to choose among the many programs offered. On the clinical programs there were about 500 presentations. Herein has developed a source of embarrassment for the Editor of the *ANNALS* as well. In its present convenient size, with the scientific material limited to approximately 1,500 pages for a year, the *ANNALS* can publish about 140 papers in each annual volume. The General Sessions provide about 65 papers, which are considered primarily to belong to the College and already earmarked for the *ANNALS*, if suitable. Due consideration must be given to the continual influx of manuscripts throughout the year from which choice must be made, for the pages of the *ANNALS* must not be restricted to material presented at the Annual Session. If, from this group of material, an amount is chosen equal to that derived from the General Sessions, it is evident at once that but few papers from the clinical programs can be published. This is greatly to be regretted for many of the clinical presentations have been quite as significant and as admirably done as those upon the general program. So great is the total volume of material available that any increase in the size of the *ANNALS*, within reasonable limits, could not appreciably relieve the situation.

CIVIC PRIDE AND PUBLIC HEALTH

Municipalities may properly boast of their natural advantages, their parks, public buildings, and commercial and industrial development, but one of the best measures of the intelligence, so-

cial-mindedness and governmental efficiency of a community is its public health record. Too often claims in this field are presented only as generalities, expressed by such terms as 'healthy,' 'healthful,' or 'salubrious.' The Journal of the American Medical Association has rendered an important service in this respect by the publication of an annual comparative survey of the typhoid fever death rates in the large cities of the United States. The twentieth report* in this series has recently appeared. It is particularly the group of food- and water-borne diseases which would appear to provide the best index of the success of the public health endeavor of a community. In the report of the survey to which reference has been made, twelve cities of more than 100,000 population are placed on the honor roll as having had no deaths from typhoid fever during the year 1931. These are Cambridge, Des Moines, Fall River, Flint, Long Beach, Lynn, Reading, Somerville, South Bend, Utica, Waterbury, and Wichita. Fifty additional cities had rates ranging from 0.1 to 1.9 deaths per hundred thousand, and five of these reported that all of their typhoid deaths were of nonresidents. The non-resident deaths create a problem for it is obviously as unfair to exclude certain of them as it is to include all. A uniform and fair method of distributing them is not available. Another element of unfairness is introduced by the necessary inclusion of the post-vacation cases. This problem is world wide. It is the chief source of typhoid

*Typhoid in the large cities of the United States in 1931, Jr. Am. Med. Assoc., 1932, xcii, 1550-1552.

morbidity and mortality in many large cities—Vienna, for instance. Perhaps the inclusion of deaths from typhoid fever in the resident population when the infection has been acquired away from home, is justifiable on the ground that the community shares the responsibility of securing protective vaccination for its citizens who seek a more primitive mode of life for their vacation period. So low is the total number of deaths from typhoid fever in most communities, a single sharply localized outbreak may play havoc with an otherwise good record. Twenty out of the thirty-one deaths in Cleveland in 1931 occurred in an outbreak at the State Hospital for the Insane. This institutional epidemic gave Cleveland a rate of 3.4, while without it the rate would have been 1.2. A low rate, i.e., less than 1.0 per hundred thousand, in a large city may indicate a greater achievement than a 0.0 rate in

a community of much smaller size. The most gratifying results are those which show a consistent improvement over a period of years in the course of which a relatively high rate has been brought down to the minimal figures of the first rank. Milwaukee, for instance, has changed a rate of 27.0 for the period 1906-1910 to 0.3 for 1931. Chicago had a rate of 15.8 in 1906-1910, and of 0.4 in 1931. Cincinnati has advanced from a rate of 30.1 in 1906-1910 to 0.4 in 1931. Many such examples exist. Comparative studies of the type presented in this survey lead to a very proper spirit of emulation among municipalities. This stimulating analysis can be applied not only to morbidity and mortality from infectious diseases but also to such public health problems as arise from automobile accidents, injuries associated with crimes of violence, and suicide.

Abstracts

Cancer and Tuberculosis, with some Comments on Cancer and Other Diseases. By EDWIN B. WILSON and HELEN C. MAHER (Am. Jr. of Cancer, 1932, xvi, 227-250.)

From pathological and epidemiological evidence opinions at variance with one another have been arrived at in respect to the simultaneity of cancer and tuberculosis. Some have maintained that cancer and tuberculosis are antagonistic, some that one disease favors the occurrence of the other, and some that the incidence and progress of the two conditions are independent. (This question has been considered previously in the ANNALS 1929, III, 495-500, and 1929, III, 501.) The difficulties involved in arriving at a sound judgment and the various statistical fallacies which must be avoided or mini-

mized are considered in the course of a mathematical treatment of the problem. It was concluded that there seems to be little or no evidence in favor of an antagonism or dissociation between cancer and tuberculosis and a considerable variety of evidence in favor of a slight degree of positive association between the two. Until better estimates of morbidity rates are available one should not be dogmatic over the matter and may well admit that for practical purposes cancer and tuberculosis may be regarded as independent. There seems to be considerable evidence that cancer of the esophagus is associated with pulmonary tuberculosis, as might perhaps be natural if the condition resulted in a long-continued malnutrition. At present there seems to be

no material which should lead to a judgment as to whether cancer and tuberculosis tend to originate in the same persons because of constitutional diathesis, or whether the association might result merely from an invasion of one of the processes by the other or a lowered resistance to the progress of one of the diseases owing to a debilitation by the other

Lead Poisoning in Children By H S MITCHELL, M D (Canad Med Assoc Jr, 1932, xxi, 546-549)

Lead poisoning in children exhibits certain peculiarities which require emphasis. Unlike the usual occupational hazards of adults, the exposure is more subtle. The juvenile system reacts more severely to a much smaller exposure, and the manifestations of intoxication are different. Except in rare instances of food-poisoning, lead is usually acquired as a manifestation of pica. Lead painted chairs, toys, and cribs [also porch railings, Editor] usually furnish the source. Such objects may be found to be devoid of paint in the areas which can be reached by the mouth. Children with lead poisoning are usually more or less irritable, but they seldom complain of colic. Constipation is almost invariably present, but seldom remarked upon by the parents unless they are questioned about it. There is usually some pallor. A lead line may be present, but less constantly than in adults. Peripheral neuritis frequently develops, and the legs are more often attacked than the upper extremities, in contrast to adult cases. Most important of all are the frequent cerebral manifestations which may be abrupt in onset. Two cases are presented illustrative of lead poisoning in children. One was referred as a case of poliomyelitis because of wrist- and foot-drop, and the other for generalized convulsions of sudden onset. The second case showed a heavy epiphyseal line upon x-ray examination. Treatment is discussed with due regard to the principles of preliminary concentration and fixation of the lead in the bones (especially important in presence of neurological crises) and subsequent slow elimination.

Coronary Disease in 100 Autopsied Diabetics By M H NATHANSON, M D

(Am Jr Med Sci, 1932, clxxviii, 495-503)

Since the discovery of insulin, the clinical picture of diabetes has been changing. Whereas before, malnutrition, infection, acidosis, and coma were the chief dangers, vascular disease is now playing a greater part. Joslin has reported that since the introduction of insulin the deaths from vascular disease in diabetics have increased from 28 to 47 per cent. In the present study the records of 100 diabetics were analyzed with special reference to the cardiovascular pathology. The coronary arteries were considered as diseased only when there was marked sclerosis with definite narrowing and partial obliteration of the lumen of one or more large branches. The results were controlled by comparison with the incidence of coronary sclerosis in general autopsy material. The entire series of 100 autopsies upon diabetics showed an incidence of severe coronary disease of 41 per cent. Above the age of 50 years the incidence is 52.7 per cent as compared with 8 per cent in a series of non-diabetics of the same age. The frequency of coronary disease was found to be almost as high among the female diabetics as among the male. In diabetics with gangrene, the incidence of coronary disease was higher than in the uncomplicated cases. The essential cardiac lesion in diabetes is coronary sclerosis. Other types of cardiac disease are of relatively rare occurrence.

Renal Function in Exophthalmic Goiter and Myxedema By J LERMAN, M D, and A J BROGAN, M D (Endocrinology, 1932, xvi, 251-256)

Because of a number of circulatory antitheses between exophthalmic goiter and myxedema it seems probable on purely *a priori* grounds that the effect would be to increase renal function in exophthalmic goiter and to decrease it in myxedema. A total of 75 patients with exophthalmic goiter and 22 with myxedema were tested by means of the phenolsulphonephthalein test as described by Rowntree and Geraghty. It was found that the renal function of myxedema patients, as determined by this method, is slightly but consistently lower than that of exophthalmic goiter patients in all age groups except in

the group 60 years of age and over. The function in both diseases is probably within normal limits. In exophthalmic goiter renal function varies with age. Up to the age of 50 the function is more or less constant, but after 50 it diminishes rapidly. In the smaller group of myxedema patients studied, such a correlation with age did not appear. No relationship was found between the degree of phthalein excretion in exophthalmic goiter and myxedema on the one hand and the basal metabolic rate or the degree of anemia on the other. A slight relationship between phthalein excretion and pulse pressure was found in myxedema only. Thus the data presented offered no support to the concept that permeability of renal tissue is significantly altered in hyperthyroidism or myxedema.

The Dynamic Bronchial Tree By CHARLES C MACKLIN, M.D. (Am Rev Tuberculosis, 1932, xxv, 393-417)

An attempt is made to visualize the *locus* of pulmonary tuberculosis. The purely conducting part of the bronchial tree (that is everything up to, and including, the fine, smooth-walled bronchioles) is envisaged as undergoing a lengthening with inspiration and a shortening with expiration, and the details of this process are explained with diagrams. The peculiar shape and mode of action of the pleural cavity make it necessary to shift the lower part of the lung during inspiration in a downward, forward and outward direction, if the part above and behind the hilum is to expand properly. The root of the lung is of very great importance in this movement, of which the reverse phase is seen in expiration. It is suggested that the normal flexibility of the root may be impaired from disease processes, and that this will hamper lung ventilation, especially in that part lying above and behind the hilum. The advisability of ascertaining the normal range of movement in the root, particularly in children, is stressed, and the possible relation of interference with this movement to pulmonary tuberculosis advanced. (Author's abstract)

A Thyroid Hormone in the Blood and Urine in Graves' Disease By LEO R HIMMEL-

BERGER, Ph.D. (Endocrinology, 1932, xvi, 264-266)

In addition to applying the biological test described by Dresel to the blood of 24 patients diagnosed clinically as exophthalmic goiter, the urine of 17 of the same group was similarly investigated. In but 13 of these did the mice live to complete the test. The hormone test on the urine was positive in 10, indefinite in 1, and negative in 2. These two patients lacked the lymphoid tissue in the thyroid which is considered indicative of Graves' constitution. It was concluded that when the blood serum or urine from patients with Graves' disease is injected into mice, a substance capable of disturbing liver function can be demonstrated. In the limited number of cases studied, the presence of the hormone was found to parallel the presence of lymphoid tissue in the resected thyroid glands, thus lending further support to the view that lymphoid areas are an essential part of the pathological picture in Graves' disease. It is suggested that the demonstration of this hormone in the urine or blood serum might be useful as an aid in differential diagnosis and that the method should prove to be of value in the experimental study of Graves' disease.

The Distribution of Blood Cholesterol in Cancer By HELEN R DOWNES, Ph.D., and GEORGE T PACK, M.D. (Am Jr of Cancer, 1932, xvi, 290-296)

Various studies of the cholesterol content of the blood in cancer have been undertaken from time to time. One of the most promising results was the observation of Mattick and Buchwald, in 1928, that in 85% of the 100 cases of cancer studied by them, the cholesterol content of the plasma was found to be higher than that of the whole blood, while 80% of the healthy persons studied showed this relationship reversed. In the present investigation it was found that there was no constant relationship between the concentration of cholesterol in the whole blood and in the plasma in a series of 63 cases of malignant tumors and allied blood diseases. The cholesterol content of the blood was not increased above normal in the presence of cancer.

Reviews

The Practitioners Library of Medicine and Surgery Supervising Editor, GEORGE BLUMER, M A (Yale), M D, F A C P, David P Smith Clinical Professor of Medicine, Yale University School of Medicine, Consulting Physician to the New Haven Hospital *Volume I Anatomy and Physiology as Applied to Practical Medicine* Associate Editors HARRY BURR FERRIS, B A, M D, E K, Hunt Professor of Anatomy, Yale University School of Medicine, and HOWARD W HAGGARD, M D, Associate Professor of Applied Physiology, Sheffield Scientific School, Yale University xlv + 1271 pages, 344 illustrations *Volume II The Technic of Clinical Medicine* Associate Editor, JOHN T KING, JR, A B, M D, F A C P, Associate in Clinical Medicine, Johns Hopkins University School of Medicine xli + 984 pages, 227 illustrations 1932 D Appleton and Company, New York and London Price \$10 00 a volume

The two volumes under review are the first to be issued in The Practitioners Library of Medicine and Surgery. The entire set will consist of twelve volumes of which the last will be a composite index. Although each volume covers a unit area in the field of medical practice the entire set is so correlated as to present all that the editorial staff considers fundamental and essential. There are certain objections that are currently urged against such encyclopediac systems of medical practice, such as that they soon become out of date and that, after all, the very point upon which one wishes information is seldom covered. These objections of necessity have something of truth in them. But carefully selected material brought up to date by those who are experienced in its practical applications is rarely set aside within a short period of time. No one expects a medical text to be a complete guide throughout a lifetime. Judged as a piece of laboratory equipment, such a set

as The Practitioners Library should be expected to depreciate, but the practitioner will find that the rate of depreciation to be charged off is very much less than that which he must apply to most of the mechanical aids which he puts in his garage and in his examining room. As to completeness, each of the more than two hundred contributors has been chosen for his special fitness for presenting his subject. That must be the chief earnest of inclusion of the essentials. Brief bibliographic lists at the end of each chapter direct the reader to the chief sources of more detailed information. This set is not planned for the medical teacher or investigator in close contact with a large medical library. Rather, as its title states, it is for the practitioner. For him such a work is nearly indispensable. It is quite impossible for him to surround himself with separate monographic works to cover the entire field of his work. Even if he has many of them at hand, he can have a working familiarity with but a few. Hence is evident the value of an elaborately indexed, well-considered presentation of the entire range of medical practice.

Volume I Anatomy and Physiology as Applied to Practical Medicine Seven chapters are devoted to anatomy and twenty to physiology. Any detailed consideration is impossible. The authoritative position of the authors responsible for the individual chapters is indicated by the fact that Davenport writes on Heredity, Blumer, on Constitutions, Eyster, on Physiology of the Circulation, Henderson, on Respiration, Best, on Pancreatic Function, Thomson and Collier, on the Endocrine Glands, Gay, on Infection and Immunity, and Karsner, on Inflammation, to mention but a few.

Volume II The Technic of Physical and Laboratory Examination in Clinical Medicine In twenty-seven chapters the methods of examination in clinical medicine from History Taking to Oral Diagnosis, are sys-

tematically presented by authors equally as eminent in their respective fields as those contributing to the first volume. Naturally, there is no occasion for giving detailed directions for all bacteriological and histopathological procedures, but those considerations which will best enable the practitioner to secure effective cooperation from the laboratory experts to whom he must occasionally appeal are fully set forth.

Each volume is indexed separately in anticipation of the final composite index. The format is practical, and well chosen illustrations are liberally used.

Clinical Roentgen Pathology of Thoracic Lesions, by WILLIAM H. MEYER, M.D., Professor of Roentgenology in the New York Post-Graduate Medical School of Columbia University, and Director of Roentgenology in the New York Post-Graduate Hospital. Octavo, 272 pages, 183 illustrations. Lea & Febiger Co., Philadelphia, 1932. Price \$6.00.

Rarely does one encounter a book written for specialists which is as valuable to the internist, the surgeon and to all those working in clinical medicine as this volume, the first of a series, each devoted to some major division of roentgenology. As the title indicates, the discussion is here limited to diseases of the thorax so that after an introductory resumé of general roentgenological principles, separate sections are devoted to diseases of the thoracic cage, special diseases of the respiratory system, lesions of the heart and pericardium, and the esophagus and subphrenic organs in relation to intrathoracic pathology. In general, the material of these sections is treated in a systematic manner using such subheadings as disturbances of development, inflammation, neoplasms, etc. In terse, lucid sentences the roentgenological features of each type of disease process are given together with sufficient information of a gross pathological nature to demonstrate the physical bases of the deviations in illumination and configuration observed. The utilization of a large number of illustrations makes the work essentially an atlas of this division of roentgenology. The many white-on-black line plates are strikingly effective both from the

straightforward simplicity of their execution and the superior press work in evidence. These complement and immeasurably aid the explanation of the many half-tone reproductions of roentgenograms, the latter being distinguished for their wealth of detail and delicacy of tonal gradation. Not the least among the many excellent features of this book is the detailed index giving the pages for the main discussion together with the pagination of all other important collateral developments. By this means the bulk of the volume has been maintained at a minimum, since repetition has been almost entirely avoided. Considering the compactness of the volume, it would appear that the publishers, in setting a price for the book, have anticipated a far more limited sale than it deserves; for all those having any contact whatever with roentgenological interpretation will find here a compendium of the most useful information.

A Hand-Book of Ocular Therapeutics. By SANFORD R. GIFFORD, M.A., M.D., F.A.C.S., Professor of Ophthalmology, Northwestern University Medical School, Chicago, Illinois, attending Ophthalmologist, Passavant Hospital, Wesley Memorial Hospital, Evanston Hospital. 272 pages, 36 engravings. Lea & Febiger, Philadelphia, 1932. Price, \$3.25.

This is an outstanding work done by a man whose wide clinical experience and intimate association with his father, Harold Gifford, have given him a firm basis for reliable opinion. The book deals with the various therapeutic measures in a clear concise manner, giving his personal clinical experiences where there are conflicting opinions. The more recent advances are discussed giving special technique and illustrations for procedures not yet commonly followed. The section devoted to anesthesia is complete and well illustrated. Drugs are discussed from the standpoint of preparation, properties and administration, and those most commonly used are listed in a convenient manner. The present status of tuberculin therapy is made clear. The preparation and dosage are listed. The uses of phototherapy, diathermy, and roentgen ray are well covered. Foreign protein is given

full consideration in the treatment of iritis and uveitis. The author is particularly enthusiastic in his treatment of gonorrheal ophthalmia by this method. It is doubtful, however, if other experienced clinicians will discard the use of mild silver-protein in this and other purulent ophthalmias. Copper stick is recommended for treatment of trachoma in the early stages. The book covers in condensed form a great amount of work in the field of ocular therapeutics. Adequate bibliographies are provided should the reader desire further information. The value of Dr Gifford's handbook is unquestionable and practically every ophthalmologist will find it useful.

CECIL LEPARD, M D

Recent Advances in Bacteriology and the Study of the Infections. By J HENRY DIBLE, M B (Glas), F R C P, Professor of Pathology in the University of Liverpool, Late Professor of Pathology in the University of London, and Professor of Pathology and Bacteriology in the Welsh National School of Medicine. Second edition. xi + 476 pages, 29 illustrations. P. Blakiston's Son and Co, Inc, Philadelphia, 1932. Price \$3 50.

Like many others of the Recent Advances Series, the member dealing with bacteriology has required a new edition although the former one has been out but three years. This is not to be wondered at for bacteriology, which some had come to look upon as a well-tilled, and all but exhausted, field, is rapidly developing aspects which, while not entirely new, are nevertheless setting off the new bacteriology rather definitely from the old. New sections on certain of the virus diseases, Brucella infections, the flocculation tests for syphilis, the Salmonella group, and antigenic structure have been required. Throughout, the text has been reworked in the light of the newer developments with special attention to the streptococcus group, bacterial variation, the bacteriophage, B C G, and specific soluble substances of the pneumococci and other bacteria. The author weighs the presumptions in regard to the Lubeck disaster and without drawing a fixed conclusion writes, "A slowly increasing body of evidence which supports Petroff's views

of the constitution of B C G make[s] it possible that some special conditions obtaining during the culture of the vaccine at Lubeck may have caused the emergence of a virulent strain." Nor is the above sentence quoted to call attention to the ungrammatical verb, for the book is unusually free from errors in agreement and in typography. Rather was it quoted with approval as indicating a conservative attitude of quasi-acceptance of a view generally unpopular. This book can be heartily recommended to every practitioner of medicine who must keep informed of the rapid transformation in bacteriology but who obviously cannot seek this widely disseminated information out for himself from the original sources. It is also an invaluable reference book for medical libraries of all types, whether in teaching institutions or hospitals.

Functional Disorders of the Gastrointestinal Tract. By WILLIAM GERRY MORGAN, M D, F A C P, Professor of Gastroenterology, Georgetown University Medical School, Consulting Physician, Georgetown University Hospital, Garfield Memorial Hospital, and Gallinger Hospital, Washington, D C. xii + 259 pages, 32 illustrations. 1931, J B Lippincott Company, Philadelphia and London. Price \$5 00.

This concise, practical manual of gastrointestinal functional disorders is a unit in the Everyday Practice Series which is being brought out under the Editorship of Harlow Brooks, M D, F A C P. It is covered with the attractive *fac simile* antique binding characteristic of this series. Gastrointestinal disorders with demonstrable tissue changes are excluded from the scope of this manual, yet the so-called "functional" diseases play such a large part in everyday medical practice that a work devoted entirely to them is amply justified. In the words of the distinguished editor of this series, "This little book is designed especially to consider these disturbances of the gastrointestinal tract in such a manner as to make their recognition and proper management plain and clear. The book has been prepared by a practitioner widely known especially for his therapeutic skill in the management of cases of diseases of the gastrointestinal

tract" Numerous citations of illustrative cases and full discussions of treatment add to the interest and value This book deserves a wide circulation

Varicose Veins with Special Reference to the Injection Treatment By H O McPHEETERS, M D, F A C S, Director of the Varicose Vein and Ulcer Clinic, Minneapolis General Hospital, Attending Physician New Asbury, Fairview, and Northwestern Hospitals, Minneapolis, Minn Third revised and enlarged edition 285 pages, 62 illustrations F A Davis Company, Philadelphia, 1931 Price \$4 00

For this third edition of McPheeter's work on Varicose Veins various sections

have been rewritten and considerable new material added While intended particularly as a guide to the treatment of this condition by the injection method and therefore giving considerable space to the essential technical details, there are a number of subjects discussed which are of interest to the general practitioner and to the internist Such are etiology, the reasons for the comparative rarity of pulmonary infarctions following the induction of thrombosis, coincident vascular complications, the management of varicose ulcer and the elephantoid condition of the lower leg due to lymphatic obstruction The book is well written, well illustrated and well printed

College News Notes

MINUTES OF THE BOARD OF REGENTS

San Francisco, Calif

April 4, 1932

(The following items are abstracted from the official minutes)

The Board of Regents of the American College of Physicians met and was called to order at the Palace Hotel, San Francisco, Calif, at 11 00 A M, by the President, Dr S Marx White, Minneapolis, Minn

The following were present Dr S Marx White, Dr James R Arneill, Dr David P Barr, Dr Walter L Bierring, Dr George E Brown, Dr James B Herrick, Dr Charles G Jennings, Dr Clement R Jones, Dr Noble W Jones, Dr J C Meakins, Dr James H Means, Dr John H Musser, Dr George Morris Piersol, Dr Maurice C Pincoffs, Dr Francis M Pottenger, Dr W Blair Stewart, and Mr E R Loveland, Executive Secretary

President White spoke briefly concerning the completed arrangements for the meeting He expressed the opinion that the subject of the next meeting place should be carefully studied, and that the meeting for 1933 should be held in a center which would attract a large attendance

The Executive Secretary read abstracted Minutes of the last meeting of the Board of Regents, which were approved as read

The Executive Secretary read the following excerpt from a letter addressed to President White from Dr Oswald T Avery

"Confirming my recent telegram, may I again tell you how deeply I appreciate the honor conferred on me by the American College of Physicians As the first recipient of the award, I feel particularly complimented, especially so since the recognition comes from a distinguished group of clinicians as an expression of their regard and appreciation of research in one of the allied sciences of medicine In giving this distinction to the work in which I have been privileged to share, I am conscious that in even larger measure they are paying a high tribute to the spirit and accomplishment of all who by observation and experiment are attempting to add to our knowledge of disease

"Thank you very much for your generous allotment of forty minutes for my address I feel, however, that I may be encroaching upon time that might more fittingly be given to others on the program In fulfilling the conditions of the award, I shall, of course, be happy to comply with your request, and on this occasion, if you so desire, suggest the following title for my remarks, "The Rôle of Specific Carbohydrates in Pneumococcus Infection and Immunity"

Resignations of the following were duly accepted

Dr William Willis Anderson (Fellow), Atlanta, Ga
 Dr L R DeBuys (Fellow), New Orleans, La
 Dr Rufus T Dorsey (Fellow), Atlanta, Ga
 Dr G C Kilpatrick (Fellow) Mobile, Ala
 Dr William Magner (Fellow), Toronto, Ont, Can
 Dr Leon F Shackell (Fellow), New Brunswick, N J
 Dr Stewart H Welch (Fellow), Birmingham, Ala
 Dr George S C Badger (Associate), Boston, Mass
 Dr R Alexander Bate (Associate), Louisville, Ky
 Dr Jeter C Bradley (Associate), Washington, D C
 Dr Stephen Cahana (Associate), Milwaukee, Wis
 Dr L E Elliott (Associate), New Market, Iowa
 Dr Thomas A Foster (Associate), Portland, Maine
 Dr Joseph M Heller (Associate), Washington, D C
 Dr Albert Kaufman (Associate), Wilkes-Barre, Pa
 Dr John D Matz (Associate), Allentown, Pa
 Dr David N Schaffer (Associate), Chicago, Ill

In reply to an inquiry concerning the collection of dues for 1932, the Executive Secretary reported that he had distributed a letter with all bills on Jan 1, suggesting that any one who found it impossible to pay his dues promptly might arrange through the Executive Offices for temporary deferment, or payment in monthly installments of said dues. Many letters of appreciation had been received from members, and, undoubtedly, a number of resignations were avoided.

Upon recommendation of the Committee on Credentials the following physicians were elected to Fellowship

Allen, William Herschel, Fort Sam Houston, Texas

Amberson, J Burns, Jr, New York, N Y
 Armstrong, Eugene Lawson, Los Angeles, Calif
 Ash, Wilfrid Anthony, Seattle, Wash
 Baltzan, David M, Sashatoon, Sask, Can
 Barnhart, Grant Samuel, Washington, D C
 Benson, Robert Louis, Portland, Ore
 Brooksher, William Riley, Jr, Fort Smith, Ark
 Brown, Robert Osgood, Santa Fé, N M
 Callaway, Guy Drennan, Springfield, Mo
 Carbonell, Arturo, Manila, P I
 Carley, Paul Sterling, New York, N Y
 Cassel, Homer Deeter, Dayton, Ohio
 Cohen, Mortimer, Pittsburgh, Pa
 Cole, William, Long Beach, Calif
 Comstock, Daniel Delos, Los Angeles, Calif
 Cook, Everett LeCompte, Denver, Colo
 Cornell, Virgil Heath, Washington, D C
 Cowie, David Murray, Ann Arbor, Mich
 Crawford, Paul Miller, Denver, Colo
 Curtis, Arthur Covell, Ann Arbor, Mich
 Dart, Raymond Osborne, Ancon, C Z
 Davis, Jay Conger, Minneapolis, Minn
 Davis, Robert Gaylord, San Diego, Calif
 Denton, William, Hot Springs Nat'n Park, Ark
 Faust, Daniel Bascom, San Francisco, Calif
 Gardam, Joseph Wilham, Newark, N J
 Grant, Brooks Collins, Fort Sam Houston, Texas
 Greenbaum, Sigmund S, Philadelphia, Pa
 Gregg, Donald, Wellesley, Mass
 Guardia, Tomas Guardia, Panama, R. P
 Haines, Edgar Fremont, Washington, D C
 Henderson, George Dallas, Holyoke, Mass
 Hill, Harold Phillips, San Francisco, Calif
 Howard, Leroy Taylor, Fort Sam Houston, Texas
 Hudson, Fredrick Edward, Stamford, Texas
 Hyland, Clarence Michael, Los Angeles, Calif
 Kern, Richard Arminius, Philadelphia, Pa

La Barge, Oza Joseph, Salt Lake City, Utah
 Ledbetter, Paul Veal, Houston, Texas
 Lowry, Robert Henry, Fort Sam Houston, Texas
 Lutterloh, Charles Hartzell, Hot Springs Nat'l Park, Ark
 Madigan, Patrick Sarsfield, Washington, D C
 McKie, Alva Burton, Manila, P I
 Mebane, Douglas Hamilton, El Paso, Texas
 Moffitt, Herbert Charles, San Francisco, Calif
 Newcomb, Warner Hames, Jacksonville, Ill
 Noble, Mary Riggs, Harrisburg, Pa
 Oginsky, Maxim Alexander, Saratoga Springs, N Y
 Olch, Benedict, Dayton, Ohio
 Olmsted, Bertram Henry, San Francisco, Calif
 Otto, Frank Wesley, Los Angeles, Calif
 Perlberg, Harry James, Jersey City, N J
 Pinner, Max, Tucson, Ariz
 Pollock, William Cramer, Denver, Colo
 Quickel, Herbert Lee, Denver, Colo
 Rawls, William Bryant, New York, N Y
 Rice, William Frederick, San Francisco, Calif
 Roberts, Frank Lester, Trenton, Tenn
 Robeson, David Loran, Fort Monroe, Va
 Ross, William Hugh, Brentwood, N Y
 Rothschild, Karl, New Brunswick, N J
 Ridsill, Hillyer, Jr, Charleston, S C
 Ruschhaupt, Louis F, Milwaukee, Wis
 Rush, Homer P, Portland, Ore
 Sale, Charles Wallace, Fort Sill, Okla
 Schumacher, Irwin Clement, San Francisco, Calif
 Sellers, Erle Dees, Abilene, Texas
 Schroeder, William F, Rock Island, Ill
 Sloan, Andrew, Utica, N Y
 Sweany, Henry Claris, Chicago, Ill
 Traynor, Raymond Leo, Omaha, Nebr
 Van Valzah, Shannon Laurie, Denver, Colo
 Waldbott, George L, Detroit, Mich
 Wchenkel, Albert Michael, Detroit, Mich
 Weis, Clifford Robert, Dayton, Ohio
 Wetterberg, Louis F, Woodbridge, N J

White, Samuel Augustus, Fort Benning, Ga
 Wile, Udo Julius, Ann Arbor, Mich
 Withers, Sanford Martin, Denver, Colo
 Woodland, John C, Ancon, C Z
 Woodson, Thomas D, Washington, D C

Dr Stewart, a member of the Committee on Insignia, of which Dr Edgar Erskine Hume is Chairman, gave the following report

"Our Committee will have to ask for further time for our final and complete report on the matter of academic dress. The reason for this is that the whole subject is coming up for reconsideration in Great Britain and also in the United States. I have been in touch with some of those who take particular interest in this subject, and am told that it would be wise for the American College of Physicians to wait until after June 1 to make a decision, as otherwise it might become desirable later to make a change. If other American academic and scientific bodies, as well as universities, are to reconsider all this, we should, I believe, await their report before making ours."

(Signed) Edgar Erskine Hume, Chairman

It was regularly moved and seconded that the above report be approved and placed on file

APRIL 6, 1932

The Board of Regents of the American College of Physicians met and was called to order at the Palace Hotel, San Francisco, Calif, at 12 35 P M, by the President, Dr S Marx White, Minneapolis, Minn

The following were present: Dr S Marx White, Dr James R Arneill, Dr David P Barr, Dr Walter L Bierring, Dr George E Brown, Dr James B Herrick, Dr Charles G Jennings, Dr Clement R Jones, Dr Noble W Jones, Dr J C Meakins, Dr James H Means, Dr John H Musser, Dr George Morris Piersol, Dr Maurice C Pincoffs, Dr Francis H Pottenger, Dr W Blair Stewart, and Mr E R Loveland, Executive Secretary

The Executive Secretary read a letter from Dr S D Van Meter, Chairman of the Effort and Invitation Committee of the American Association for the Study of Goiter, suggesting, first, that the American College of Physicians join other national

medical and surgical societies in extending an invitation for the Third International Gorter Conference to come to America in 1937, and, second, that the American College of Physicians appoint an official delegate to join the American delegation to the International Gorter Conference at Berne, Switzerland, at its next meeting to co-operate in bringing the International Gorter Conference to America in 1937

After discussion, on motion of Dr Biering, seconded by Dr Arneill, and regularly carried, it was

RESOLVED, that the Executive Committee be empowered to appoint a delegate to represent the College at Berne, Switzerland, in connection with the meeting of the International Gorter Association without expense to the College

ASSOCIATES

On behalf of the Committee on Credentials, Dr Piersol presented the list of candidates recommended by the Board of Governors for election to Associateship. The following physicians were duly elected

Alexander, Archibald Addison, Oakland, Calif

Arrendell, Cad Walder, Ponca City, Okla

Baer, Ridgely Waters, Frederick, Md

Ball, Ralph G, Manhattan, Kansas

Bell, John Kenner, Detroit, Mich

Blitch, Clifford G, Jacksonville, Fla

Bloom, Benson, Tucson, Ariz

Brand, Alonzo F, Fayetteville, N Y

Briskman, A Lee, Colorado Springs, Colo

Burkley, George Gregory, Rochester, Minn

Carman, Henry Franklin, Dallas, Texas

Carns, Marie L, Madison, Wis

Castell, Louis B, Washington, D C

Chernaik, Samuel Julius, New Britain, Conn

Chrisman, William Walter, Macon, Ga

Condry, Raphael Joseph, Elkins, W Va

Cronwell, Bernhard J, Jr, Austin, Minn

Deegan, John Kenneth, West Haven, Conn

Denison, Robert, Harrisburg, Pa

Durgin, Lawrence Newton, Amherst, Mass

Dr. Bernard G. New Orleans, La

Esbenshade, John H, Lancaster, Pa
Fineman, Abraham Harold, New York, N Y

Flack, Russell Allen, LaFayette, Ind

Flipse, Mathew Jay, Miami, Fla

Foord, Alvin G, Pasadena, Calif

Fregeau, Aime N, San Francisco, Calif

Gardner, Walter P, St Paul, Minn

Goldbloom, A Allen, New York, N Y

Goldsmith, Leon A, Portland, Ore

Goldstein, Eli, New York, N Y

Gordon, Douglas M, Ponca City, Okla

Griffith, George Cupp, Philadelphia, Pa

Hannah, William Sessions, Montgomery, Ala

Harding, George T, III, Columbus, Ohio

Hargrove, Marion Douglas, Shreveport, La

Harmeier, John Watson, Rochester, Minn

Harvey, James E, Pasadena, Calif

Hastings, Gordon, Little Rock, Ark

Hekimian, Ivan, Buffalo, N Y

Hiemstra, Wybren, Missoula, Mont

Hookey, John A, Sr, Detroit, Mich

Hunter, Melville Wallace, Monroe, La

Huntington, Herbert Arthur, Los Angeles, Calif

Iisley, Morrill Leonard, Claremont, Calif

Johnston, John M, Pittsburgh, Pa

Kirby, Dunne Wilson, Philadelphia, Pa

Kramer, Louis Irving, Providence, R I

Lane, Lowell L, Philadelphia, Pa

Lawson, Herman A, Providence, R I

Lee, Russel Van Arsdale, Palo Alto, Calif

L Levy, Frank E, Philadelphia, Pa

Levin, Charles Morris, Richmond Hill, N Y

Lewis, Paul John, Yakima, Wash

Lichty, John Max, Pittsburgh, Pa

Markel, Albert G, Paterson, N J

McLain, Ernest K, Louisville, Ky

Menard, Olive Joseph, Boston, Mass

Milstead, Laurence C, Allentown, Pa

Mitchell, Louis Albert, Newark, Ohio

Murphey, Bradford J, Colorado Springs, Colo

Nakada, James Robert, St Louis, Mo

Norris, Henry Martin, East Orange, N J

Nussbaum, Sydney, Brooklyn, N Y

Osgood, Carroll W, Milwaukee, Wis

Pratt, Orlyn Bernard, Los Angeles, Calif

Reed, Marjorie E, Plymouth, Pa
 Safarik, Lumir Robert, Denver, Colo
 Scott, Roy L, Buffalo, N Y
 Scott, Walter Roger, Niagara Falls, N Y
 Sears, Thad P, Denver, Colo
 Sexton, Daniel Leritz, St Louis, Mo
 Shaw, John A, Fayetteville, N C
 Sheehan, George A, Brooklyn, N Y
 Simons, Samuel Shirk, Lancaster, Pa
 Spannuth, John R, Reading, Pa
 Squires, Willard Haywood, New York, N Y

Stallings, Walker Eugene, Boise, Idaho
 Taylor, James Edwin Campbell, Rochester, Minn

Terrell, Caleb O, Fort Worth, Texas
 Weisler, Harry, Brooklyn, N Y
 Werner, August A, St Louis, Mo
 Wilson, James Alfred, Meriden, Conn
 Ylvisaker, Lauritz S, Newark, N J
 Ylvisaker, Ragnvald S, Minneapolis, Minn

Dr Pierson stated that no doubt there would be a question in the minds of some of the Regents as to why some candidates whose names had been proposed for Fellowship appeared on the list of Associateship candidates. The reason for this was that according to the present By-Laws, all candidates proposed after the 31st of December, 1931, must be considered first for Associateship, and serve the three to five year period before they are eligible for proposal to Fellowship, except in the case of men of great prominence and distinction, who can, by order of the Board of Regents, be elected as Fellows. In some instances, men who were just elected to Associateship last year were proposed for Fellowship this year. Such men are not eligible for election to Fellowship, because they must remain Associates for at least three years before they are eligible to be proposed for Fellowship.

The Executive Secretary presented the report on the Committee on Exhibit at the Chicago Century of Progress in 1933 as follows:

"Your Committee consisting of Dr Clement R Jones, Dr James G Carr, and Mr E R Loveland, appointed to study the advisability of an exhibit by the College at the coming exposition in Chicago, in 1933, desires to submit the following report:

"The Committee met at Rochester on Feb-

ruary 13 and spent several hours in conversation and discussion with Dr T E Finnegan, Director of Educational Films for the Eastman Kodak Company, Mr Edwards, the production manager, and Dr Jones, the scenario writer. After considerable discussion the following plan was the only one which we felt could be recommended. This plan included the use of 1½ or 2 reels which would require some twenty to thirty minutes for each complete exhibition. One reel would be designed to present in motion pictures a complete physical examination, including the estimation of the blood pressure, a urine examination, a complete blood examination, and the taking of blood for a Wassermann test.

"The design was that the first reel or the first portion of the motion picture would present the physical examination as it ought to be done by any capable general practitioner, this to be followed by a further demonstration of special methods of examination regularly used by the specialist in internal medicine.

"For instance, if the routine physical examination suggested some question about the heart, the use of chest plates, of the electrocardiograph, and of the basal metabolimeter would be indicated, if the original examination raised a question as to disease of the gastro-intestinal tract, the x-ray, gastric analysis, stool analysis, gall bladder visualization and other allied procedures might be shown on the screen. It was planned that the second reel should include roentgenology as applied to the various problems of internal medicine, the electrocardiograph, and the basal metabolimeter, laboratory tests as related to the gastro-intestinal functions, to the gall bladder and to the blood and urine, special examination of blood for nitrogenous end-products, uric acid, bile pigments, etc. It would be our purpose to present to the public these various methods of special investigation with a view to instruction as to the importance of this special equipment and particularly as to the necessity for expert guidance of all these procedures and an interpretation of the results based on the experience and scientific training of the diagnostician.

"The cost of the reels alone is likely to be in the neighborhood of \$10,000. It is probable, so we gathered from the conversation, that the motion pictures might be procured for less than this. It is also possible that they might cost more. To this must be added, if such an exhibit is undertaken, a sum for retaining one or two young men to operate the machine. It is likely that two medical students might be found for this, each for half-time work. There might be in addition some expense for unexpected repairs. The members of the Committee feel that \$10,000 is probably a

minimum figure for the expense of such an exhibit

"We have outlined a plan of procedure which might be followed if the Regents deem it advisable. However, the members of the Committee are unanimous in the opinion that the expense of such an exhibit would not be justified by the results. We all feel that in order to keep the exhibit within anything like reasonable cost the demonstration must be shortened until its value would become very questionable and our feeling is that it would be unwise for the College to undertake the exhibit proposed above."

On motion, seconded and regularly carried, it was **RESOLVED**, that the report of the Committee be approved

On behalf of the Committee on Public Relations, Dr Jennings submitted the following report

"The Committee on Public Relations has considered the report of the sub-committee on Medical Education of the Committee on Medical Care for Children of the White House Conference on Child Health and Protection presented at the meeting of the section on medical service at Washington, D C, February 20, 1931

"The report deals extensively with the subject of Pediatric Education. Your committee recommends that the American College of Physicians heartily endorse the recommendations embodied in the report of the sub-committee on Medical Education, and express its appreciation for this able work in the interest of Pediatric Education."

On motion by Dr C R Jones, seconded by Dr Musser, and regularly carried, it was **RESOLVED**, that the report of the Committee on Public Relations be and is herewith approved by the Board of Regents

Dr Pincoffs suggested that the Committee on Public Relations should have access to the editorial pages of the *ANNALS* to make public their endorsement of this work of the National Committee, if they so wish. He expressed the opinion that the Public Relations Committee would do well, instead of leaving their conclusions to be more or less buried in the Minutes of our meeting, to use the editorial pages as a means of putting before the whole College and the general medical public, the results of their investigations

The Executive Secretary reported that he had been instructed to consult counsel concerning the possibility of restraining the

Pilgren Company from using the name of the American College of Physicians in their advertising with relation to a booklet "by the late Professor E S Bishop, M D, Fellow, American College of Physicians, and Professor of Clinical Medicine" Counsel advised that since the Pilgren Company had now agreed to refer to Dr Bishop, who actually was a Fellow of the College, as the "late" Professor Bishop, no further restraint could be enforced

No action was taken by the Board of Regents on the above

The Executive Secretary presented a list of Fellows and Associates whom he recommended be dropped from the rolls, because of more than two years' delinquency, as provided in the By-Laws, the list having previously been submitted to the Board of Governors

On motion by Dr Piersol, seconded by Dr Arneill, and regularly carried, it was

RESOLVED, that the delinquent members be dropped from the rolls of the College

In reply to an inquiry, the Executive Secretary made the following membership report

Masters	5
Fellows	2286
Associates	572
Total	2863

The Executive Secretary presented the financial reports of the College for the year ended December 31, 1931, and the proposed budgets for 1932. In summarizing the financial operation of the College for 1931, he pointed out that the Endowment Fund now amounts to \$52,400 and the General Fund to \$57,166 71, or a total of \$109,566 71, whereas on January 1, 1927, the total assets were less than \$10,000

The Treasurer, Dr Clement R. Jones, commented on the work of the Treasurer's Office for the past year, and reported that \$2,325 44 additional had been paid by one of the closed banks, and that it seemed very probable that all the funds of the College in closed banks would be paid in full, and that the Exchange National Bank, in which the College had some \$5,000, would likely open for business again very soon

On behalf of the Finance Committee, Dr Jones presented the following resolution to be referred to the Committee on Constitution and By-Laws for report at the next meeting of the Board

"That, within one month after installation, the President shall appoint a Finance Committee of three from the Board of Regents, which shall be authorized to have general supervision of the finances of the College, to select banks and trust companies as depositories for all College funds, after careful investigation as to the standing and reliability of such institutions. Said Committee shall have the power to authorize such banks to receive and pay money out of College funds upon the signature of the Treasurer or some Regent authorized by the Finance Committee, to invest the surplus and endowment funds of the College in such bonds as are approved for savings banks and estate trusts in Pennsylvania and New York, or other states with equal requirements

"The Executive Secretary shall make a monthly report to the Finance Committee of all receipts and disbursements for the preceding month, and at least sixty days before the Annual Meeting the proposed budget for the coming year shall be submitted to the Finance Committee for consideration and recommendation at the Annual Meeting of the Board of Regents. All matters affecting the financial welfare of the College shall be referred to this Committee for consideration and report to the Board of Regents. The Finance Committee shall, at least thirty days before the Annual Meeting, submit to the Executive Secretary an Annual Report for submission to the Board of Regents of all moneys and investments and shall report at any other time when called upon by the Board of Regents or the Executive Committee. The Treasurer shall be ex officio a member of the Committee"

After considerable discussion, on motion by Dr Bierring, seconded by Dr Jennings, and regularly carried, it was

RESOLVED, that the report of the Treasurer be received and that the proposed resolution be referred to the Committee on Constitution and By-Laws for a report at the next meeting

Discussion followed regarding the continuance of the present Finance Committee. It was suggested that the present Committee be continued, with Dr S Marx White substituted for the term of Dr Pottenger, President-Elect

On motion by Dr Pottenger, duly seconded and regularly carried, it was

RESOLVED, that the Finance Committee for the coming year shall consist of Dr Clement R Jones, Chairman, Dr Charles G Jennings (1933), Dr James S McLester (1934), Dr S Marx White (1935), and Dr Charles F Martin (1936)

On motion by Dr Pottenger, seconded by Dr Meakins, and regularly carried, it was

RESOLVED, that the Finance Committee, at the next meeting of the Board of Regents, recommend certain banks as depositories, and that a resolution be passed delegating the banks recommended, to act as depositories, and also that the Finance Committee recommend who shall sign checks

The Executive Secretary read the report of the Committee on Constitution and By-Laws, which was as follows

"The Committee on Constitution and By-Laws at the request of President S Marx White, who suggested the desirability of Honorary Fellowships in the College, submits the following

Suggested Amendments to Constitution

"1 Add to Article III, Section 3, paragraph 1, after the word 'elect' in the second sentence the words 'Honorary Fellow and'

"2 Article IV, first paragraph Add after the word 'Masters' the following 'There shall also be (c) "Honorary Fellows" as subsequently defined'

"3 Article IV, following the sixth paragraph '(c) Honorary Fellows Upon nomination of the Board of Regents the College may elect medical men or women or scientists engaged in medical research to be Honorary Fellows Such Honorary Fellows shall have all the privileges of members excepting the right of holding office or voting They shall not pay dues nor receive the publications of the College or other similar prerequisites granted to members paying dues'

Dr Stewart stated he doubted the advisability of enacting this change, and that the general sentiment of the Committee on Constitution and By-Laws was not favorable to the adoption of the change

On motion of Dr Jennings, seconded by Dr Pincoffs, and regularly carried, it was

RESOLVED, that the report of the Committee on Constitution and By-Laws be received and that recommendations in it be deferred

It was recommended by Dr Stewart that the resignation of Dr William H Deaderick as Governor of the State of Arkansas be accepted, due to the illness of Dr Deaderick

On motion by Dr Jennings, seconded by Dr Pincoffs, and regularly carried, it was **RESOLVED**, that the resignation of Dr William H Deaderick as a member of the Board of Governors be accepted

On motion by Dr Pincoffs, seconded by Dr Bierring, and regularly carried, it was **RESOLVED**, that the present Committee on *ANNALS OF INTERNAL MEDICINE* be continued until permanent arrangements are made for a standing Committee on the journal

Dr Stewart stated that three or four of the officials in the College had recommended that the Editor of the *ANNALS* should be made an ex officio member of the Board of Regents, and that the Committee on *Annals* would be glad to co-operate with whatever action the Board desired

On motion by Dr Pincoffs, seconded by Dr Musser, and regularly carried, it was **RESOLVED**, that the matter of the Editor of the *ANNALS* being made an ex officio member of the Board of Regents be referred to the Committee on Constitution and By-Laws

The Executive Secretary announced that very cordial and complete formal invitations had been received from the cities of Pittsburgh, Chicago, Montreal and Indianapolis to hold the next Convention of the American College of Physicians in those cities

Dr Herrick, on behalf of Chicago, presented invitations from the Deans of the University of Chicago and Rush Medical College, Northwestern University Medical College, University of Illinois Medical College and Loyola University Medical College, likewise letters from Dr A R Elliott, from the Chicago Medical Society, Illinois State Medical Society and the Chicago Association of Commerce

Dr Meakins stated that Dr Martin, one of the former Presidents, had for some time been keen to have the College meet in Montreal and that they had decided to wait until it could be done properly, that he now had with him an invitation from Dr Martin and from the two Universities of Mon-

treál and the medical schools and hospitals, to hold the 1933 Clinical Session in Montreal

Dr Clement R Jones presented in detail the advantages of meeting in Pittsburgh. It was the consensus of opinion that the 1933 meeting should be held near the center of population. Dr Meakins stated that while the invitation from Montreal was for 1933 that they would be just as happy to have the meeting there in 1934, if the other members felt it would be more satisfactory to have the 1933 meeting in the United States. After considerable discussion, it was decided to defer decision as to the next meeting place until the next meeting of the Board of Regents

Adjournment

APRIL 8, 1932

The Board of Regents of the American College of Physicians met and was called to order at the Palace Hotel, San Francisco, Calif, at 12 45 P M, by the President, Dr Francis M Pottenger, Monrovia, Calif

The following were present Dr Francis M Pottenger, Dr James R Arneill, Dr David P Barr, Dr Walter D Biering, Dr George E Brown, Dr Charles G Jennings, Dr Clement R Jones, Dr Noble W Jones, Dr J C Meakins, Dr James H Means, Dr George Morris Piersol, Dr Maurice C Pincoffs, Dr W Blair Stewart, Dr S Marx White, and Mr E R Loveland, Executive Secretary

The Executive Secretary read an abstract of the Minutes of the last meeting, which was approved as read

After discussion regarding the standing Committee on *ANNALS*, on motion by Dr White, duly seconded and regularly carried, it was

RESOLVED, that a standing Committee on *ANNALS OF INTERNAL MEDICINE* be constituted to consist of three members to be appointed by the President—one for a term of one year, one for a term of two years, and one for a term of three years, and, thereafter, at the expiration of the term of each member, the President shall appoint his successor for a period of three years

There was a discussion of having a permanent Committee on Constitution and By-

Laws, whereupon on motion by Dr White, seconded by Dr Means, and regularly carried, it was

RESOLVED, that a standing Committee on Constitution and By-Laws be constituted—the President to appoint one member for one year, one member for two years, and one member for three years, and, thereafter, annually, the President, upon assuming office, shall appoint a member to succeed each member as his term expires

On motion by Dr White, seconded by Dr Piersol, and regularly carried, it was

RESOLVED, that the Executive Committee be re-elected, with the addition of Dr Walter L. Bierring to fill the place left vacant by the death of Dr Aldred Scott Warthin

The following members were therefore designated to serve on the Executive Committee Dr Francis M. Pottenger, Dr Clement R. Jones, Dr Walter L. Bierring, Dr J. C. Meakins, Dr James H. Means, Dr James Alex. Miller, Dr George Morris Piersol, Dr Maurice C. Pincoffs and Dr S. Marx White

Nominations for Secretary General were made as follows Dr William Gerry Morgan, Washington, D. C., nominated by Dr White, seconded by Dr Piersol, Dr William D. Stroud, Philadelphia, Pa., nominated by Dr Means, and duly seconded. Voting was done by ballot. The tellers, after making their count, reported Dr Morgan's election.

It was moved, seconded and regularly carried, that Dr Morgan's election be made unanimous.

Upon nomination and unanimous vote, Dr Elmer H. Funk, Philadelphia, Pa., was elected Treasurer.

Free discussion as to the next meeting place followed. It was decided that it was a matter for the Board of Regents to take action upon, and that a vote should be taken to determine the question.

The result of the voting was Chicago, 1, Pittsburgh, 3, and Montreal, 9.

Dr Jonathan C. Meakins was unanimously appointed General Chairman. It was suggested that the time of the meeting be set for some week in February, according to

the convenience of Dr Meakins and his Montreal committees.

A discussion followed concerning financial procedures in the College. Upon motion regularly made, seconded and carried, it was

RESOLVED, that the depositories for the College funds be the present depositories, the First National Bank of Pittsburgh, the Colonial Trust Company of Pittsburgh, Union National Bank of Pittsburgh, Commonwealth Trust Company of Pittsburgh and an additional bank or banks selected in Philadelphia or New York after investigation by the Finance Committee.

Dr C. R. Jones, Chairman of the Finance Committee, brought up the subject of having someone in addition to the Treasurer and the Executive Secretary authorized to sign either vouchers or checks, in case of the incapacity of either the Treasurer or Executive Secretary.

Upon motion by Dr C. R. Jones, seconded by Dr White, and regularly carried, it was

RESOLVED, that the Board of Regents empower the Chairman and the Vice Chairman of the Finance Committee to sign checks and/or vouchers for College funds, so that in case of incapacity of the Treasurer and/or Executive Secretary such funds would not be tied up.

On further motion by Dr White, seconded by Dr Stewart, and regularly carried, it was

RESOLVED, that the ex-Treasurer, Dr Clement R. Jones, be empowered to sign checks until such time as the transfer of funds is made to the new Treasurer and recorded.

Dr Clement R. Jones extended an invitation to the American College of Physicians to meet in Pittsburgh in 1934. He stated that Pittsburgh would continue preparing for the College, and that the College would not be disappointed when it finally selected Pittsburgh.

In answer to the question as to whether an Associate automatically becomes a Fellow, under the new plan, it was explained that inasmuch as the credentials or qualifications of a candidate change between the time of his election to Associateship and the time he may be proposed for Fellowship, the

Committee feels it desirable to have him re-proposed on the regular form for advancement to Fellowship at the proper time. He can be re-proposed by any Fellow of the College, seconded by another Fellow and endorsed by an Officer, Regent or Governor. The By-Laws provide that at the expiration of three years, Associates shall be notified in writing of their eligibility for proposal for

election to Fellowship within the next two years, providing they shall meet within that time the requirements necessary for Fellowship.

There being no further business, the meeting adjourned at 2 15 P M.

E. R. LOVELAND,
Executive Secretary

MINUTES OF THE BOARD OF GOVERNORS SAN FRANCISCO, CALIF., APRIL 4, 1932

(Abstracted from the official minutes.)

The Board of Governors of the American College of Physicians met and was called to order at the Palace Hotel, San Francisco, California, at 4 15 P M., by the Chairman, Dr. W. Blair Stewart, Atlantic City, New Jersey.

The following were present: Dr. W. Blair Stewart, Dr. Ernest B. Bradley, Dr. Charles H. Cocke, Dr. T. Homer Coffen, Dr. A. Comingo Griffith, Dr. Josiah N. Hall, Dr. Thomas Tallman Holt, Dr. Hans Lasser, Dr. William Gerry Morgan, Dr. G. G. Richards, Dr. Adolph Sachs, Dr. Rock Sleyster, Dr. Charles T. Stone, and Mr. E. R. Loveland, Executive Secretary.

The Executive Secretary read abstracted minutes of the last meeting of the Board of Governors, which were approved as read.

Dr. Stewart introduced Dr. Francis M. Pottenger, President-Elect, who spoke briefly on the importance of the work of the Board of Governors and the ultimate goal of the College. He said the future of the College is to be determined very largely by the Board of Governors, that a great deal of responsibility lies with the Board of Governors in passing upon the qualifications of young men proposed for membership, to encourage young men who are capable and desirable by helping them along, but not to recommend a man simply because he desires membership. Dr. Pottenger said that the following questions often arise: What is to be the future of our organization? What is its purpose? Shall we launch out into something more? What shall be our ultimate goal? His feeling was that we ought to take a firm stand

for Internal Medicine and all that it stands for, that we should be the greatest influence in America for Internal Medicine.

Chairman Stewart spoke briefly of his work as Chairman of the Board of Governors during the past year. He reported that the oldest member of the Board, Dr. Edward O. Otis, of New Hampshire, had asked to be kindly remembered to all members of the Board of Governors. Communications from other Governors who were unable to be present were also presented.

Upon request, the Executive Secretary read portions from the Constitution and By-Laws regarding requirements for admission to Associateship—especially those referring to the period of time a physician must be in active practice before he is eligible for proposal.

Upon request of Dr. Stewart, President White, who had just entered the meeting at this time, spoke briefly regarding the increased responsibility of the Board of Governors since the amendments to the Constitution and By-Laws adopted at the Boston Session in 1929 had become effective on January 1, 1932, namely, that all new members must enter the College first as Associates, and that all candidates for Associateship are passed upon first by the Board of Governors. Dr. White stated that these amendments had been incorporated in the Constitution and By-Laws because of the necessity for some mechanism by which there could be greater scrutiny and better opportunity for studying prospective Fellows of the College. The new arrangement provides that every physician in the future, except in very special cases, shall come in first

as an Associate, and shall be under the careful scrutiny of the Board of Governors and the Board of Regents for a period of three to five years before he shall be eligible for election to Fellowship. It will give the College a chance to study the physician in his relation to his profession, his responsibility, his attitude, his personality, etc.

President White further referred to another point of interest in the evolution of the College, as to whether the College should undertake functions which might be considered economic, that there will unquestionably be some drastic changes affecting medical economics, and that it is important to consider and discuss any participation the College may subsequently undertake.

Chairman Stewart read a letter and a telegram from Dr E J G Beardsley, Governor for eastern Pennsylvania, recommending that the College should elect a Governor for the State of Delaware.

Upon motion by Dr Richards, seconded by Dr Griffith, and regularly carried, it was

RESOLVED, that the Nominating Committee be requested to make a nomination for a Governor for the State of Delaware.

Dr C H Cocke, Vice-Chairman of the Committee on Credentials for Associateship, reported for that Committee in the absence of the Chairman, Dr Allen A Jones. The Committee recommended to the Board of Governors for their approval to the Board of Regents the election of 85 physicians. (A list of those recommended may be found in the minutes of the meeting of the Board of Regents for April 6, 1932.)

On motion by Dr Griffith, seconded by Dr Holt, and regularly carried, it was

RESOLVED, that the report of the Credentials Committee be received and that the candidates be recommended to the Board of Regents for election to Associateship.

The Executive Secretary then presented a list of twenty members delinquent in dues for more than two years. He stated that every possible means had been resorted to in order to collect the dues from these members, and that, as his last resort, he had notified them that they would be dropped from the rolls of the College at this meet-

ing, should their dues not be paid. This list represents those who have failed to comply with the requirements of the By-Laws, and are to be presented to the Board of Regents for being dropped for delinquency.

Upon inquiry from one of the members of the Board, Chairman Stewart explained the procedure that must be followed in order to drop an undesirable member. The By-Laws, Article XIII, Section 1, provides a method of expulsion.

Dr Lisser, Governor for northern California, suggested the desirability of sending a letter to the entire membership of Fellows, stating clearly that the College is not interested in number, but is distinctly interested in the quality of candidates, and suggesting that in the future Governors may not be put in the awkward position of being asked to endorse candidates whom they do not consider qualified for election. Dr Lisser also raised the question concerning the candidate who lives at such a distance that it is not possible for the Governor to meet or to know him personally. Chairman Stewart replied that it is, of course, desirable to contact each candidate, but if, because of distance, the Governor is not able to visit the candidate or have the candidate visit him, he should write to physicians, preferably members of the College, residing in the same community in which the candidate lives, inquiring specifically about the candidate's professional standing, medical ethics, and other relevant details helpful in determining the candidate's fitness for election.

Adjournment

APRIL 7, 1932

The Board of Governors of the American College of Physicians met and was called to order at the Palace Hotel, San Francisco, Calif., at 12 45 P M., by the Chairman, Dr W Blair Stewart, Atlantic City, N J.

The following were present: Dr W Blair Stewart, Dr Ernest B Bradley, Dr James G Carr, Dr Charles Hartwell Cocke, Dr T Homer Coffen, Dr A Comingo Griffith, Dr Josiah N Hall, Dr Thomas Tallman Holt, Dr Ernest E Laubaugh, Dr Hans Lisser, Dr Leander A Rely, Dr G

G Richards, Dr Adolph Sachs, Dr Charles T Stone, and Mr E R Loveland, Executive Secretary

The Executive Secretary presented the financial reports for the year ended December 31, 1931, and discussed them in detail

Chairman Stewart asked for expressions of opinion, individually or collectively, upon the question of where the next annual meeting of the College should be held. He reported that invitations had been received from Pittsburgh, Montreal, Chicago, Memphis and Indianapolis, and that while the meeting city would be selected by the Board of Regents, they would appreciate the recommendations of the Board of Governors. After discussion of present economic conditions, the ability of different cities extending invitations to provide necessary requirements for a Clinical Session of the College, etc, the consensus of opinion was that a central location should be selected, and that the invitations of Chicago and Pittsburgh be particularly considered.

Chairman Stewart stated that the San Francisco meeting had been one of the outstandingly successful gatherings of the College, and that much credit was due to members from San Francisco and California, generally.

On motion by Dr Cocke, seconded by Dr Bradley, and regularly carried, it was

RESOLVED, that the Board of Governors of the American College of Physicians express its appreciation and gratitude for a most excellent program given by the California men, and that this appreciation be extended particularly to Dr William J Kerr, General Chairman, and to his various Committees.

Chairman Stewart then expressed his appreciation and thanks to the members of the Board of Governors who had come to the meeting. He asked members of the Board always to bear in mind the desirability of raising the standard of the College a little higher than it was prior to the adoption of the amendments to the present Constitution and By-Laws, that Governors

should remember that while new candidates for Associateship are not required to present the qualifications for full Fellowship, no candidate should be endorsed unless he promises to qualify for Fellowship within a period of three to five years.

Dr Stewart thanked the Governors also for responding promptly to communications and inquiries from the Executive Secretary with regard to candidates, and asked them to co-operate in selecting from the Associates in the different districts those men who are eligible for proposal for Fellowship. While the College is not seeking large numbers, it is important to select from the list of Associates in the different states those men who possess outstanding qualifications and who will make good as Fellows.

On motion by Dr Bradley, duly seconded and regularly carried, it was

RESOLVED, that the Board of Governors express its appreciation of the work of the Executive Secretary, Mr Loveland.

Before adjournment, Dr Cocke, for the Committee on Credentials, requested all members of the Board to give earnest consideration to the recommendation of candidates, in an effort to assist the Committee in passing on men proposed for membership. He stated that the comments received about the same candidate are often widely different, that in many cases one Governor will heartily approve of a candidate and another Governor will have emphatic objections to the same man, making it very difficult for the Committee on Credentials to reach a decision concerning election. Dr Cocke also stated that many cards are returned stating that the candidate is "unknown", which emphasizes the need of having the Governor make thorough investigation through friends, acquaintances, or other members of the College, and to send such personal and definite information for the attention of the Committee.

Adjournment

E R LOVELAND,
Executive Secretary

GENERAL BUSINESS MEETING
OF THE
AMERICAN COLLEGE OF PHYSICIANS
SAN FRANCISCO, CALIF.,
APRIL 7, 1932

The General Business Meeting of the American College of Physicians, held in connection with the Sixteenth Annual Clinical Session in the Gold Ballroom of the Palace Hotel, San Francisco, Calif, convened at 4 45 P M, Thursday, April 7, 1932, Dr S Marx White presiding

Dr White said in part "This meeting in San Francisco has been one of the delightful experiences on the part of the members of the College. It has been a privilege to me to serve the College in the capacity of its presiding officer during the past year and have a part in the preparation of the program. This is the second meeting to use the new method of program-making by which the President makes up the national program, dividing the responsibility so that the General Chairman and the Local Committee make up the clinical program. San Francisco has given us one of the unique meetings. I was extremely anxious that during this meeting there should be an opportunity for the Fellows of the entire country to learn what 'our other metropolis' has to show."

The reading of the Minutes of the last meeting was dispensed with.

The Treasurer commented on his report which had been previously published in the *ANNAIS OF INTERNAL MEDICINE*. An interesting comparison of the finances of the organization was made. Dr Jones stated that at the time of taking over the office of Treasurer eleven years ago, there was about \$8,000 in the treasury, and that the amount in the treasury at the present time was around \$130,000. In retiring as Treasurer, Dr Jones expressed the hope that the finances would progress rapidly, and that the endowment fund might continue to increase and be sufficient to carry on such work as was done this year in presenting the John Phillips Memorial Prize. Dr Jones expressed his appreciation of the courtesies and considerations that had been shown him by the Fellows during the eleven years that he was Treasurer.

Upon motion, the report of the Treasurer was accepted.

The Executive Secretary presented his annual report, mentioning among other matters the publication of the 1931-32 Directory, with membership statistics, including 5 Masters, 2286 Fellows and 572 Associates, a total of 2863. He reported that there were twenty-eight Life Members, including the retiring President, Dr White, as the most recent one. He also reported that the registration at the Clinical Session was 1,586, of which 133 were visiting ladies. An invitation was extended to all members of the College to visit the headquarters at Philadelphia whenever they are in that City.

Dr John Dudley Dunham, Columbus, Ohio, proposed a rising vote of thanks, which was given, to the San Francisco members responsible for the splendid entertainment and magnificent program furnished.

Dr White said in part "Before relinquishing the chair, your President wants to outline one or two considerations which occurred to him during this year, and the year previous. The College has won a place in American medicine in the sixteen years of its activities. I feel strongly that the American Medical Association has its prime place in the professional and economic life of Medicine in this country, that there is a place, however, for other organizations with special interests, and a place which can be of extreme and extraordinary usefulness.

"Not only is there opportunity for professional advancement and for the study of the specific problems which a group like ours might desire to consider, in the interests of the type of work which we represent in American Medicine, but there is also an opportunity and a necessity for a study and discussion of some of the economic questions in Medicine. I have no desire to outline them at this time—I tried to outline them briefly in my address last night, but it seems to me that much as we should like to retain our clinical interests only, we will be re-

quired, through the years which are immediately ahead, to take some very definite part in the study and recommendations on economic problems. Just how that is to be brought about seems to be a very difficult matter for us to decide. I am thoroughly aware that pronouncements on economic questions in medicine are extremely difficult, our basis for understanding is different, the approach which each of us makes to various problems is so different. I think the ideals of all of us look very much in the same direction, and yet, economic considerations will be forced upon us, and only as we are in position to study them and at least to mark out what are safe and sane and effective approaches to our economic problem, can we expect to keep up with the rapid crystallization which is eventually coming to us in Medicine. How that is to be brought about, I have no recommendations to make, but this body as a whole, I feel, must be prepared and should be thinking strongly along lines other than the clinical one."

The retiring President, Dr. White, presented the incoming President, Dr. Francis

M. Pottenger, of Monrovia, Calif., who made the following remarks:

"I wish to thank you for this great honor you have conferred upon me. I never had any anticipation that I might be President of this organization. I have always worked for this organization. I have been on the Board of Counsellors and Regents since its inception. When it was brought to my notice in the beginning, I thought it was one of the greatest opportunities for Internal Medicine that had ever been offered in America, and I still think that is what we have. I have attended all the meetings since its organization, except one, and I have seen it grow in interest and in usefulness, ever feeling that this organization is fulfilling the wants of its members."

"I simply want to say to you that I will do my best. My predecessors have set a pace and I hope I can progress throughout my administration. I ask you all to help me."

In the absence of Dr. Stengel, Chairman of the Nominating Committee, Dr. Stewart submitted the following report:

"The Nominating Committee of the American College of Physicians begs to offer in nomination

For the Elective Offices

President-Elect
First Vice President
Second Vice President
Third Vice President

George Morris Piersol, Philadelphia, Pa.
Maurice C. Pincoffs, Baltimore, Md.
Charles G. Jennings, Detroit, Mich.
Noble Wiley Jones, Portland, Ore.

For the Board of Regents

(Term Expiring 1935)

Arthur R. Elliott
James B. Herrick
S. Marx White
David P. Barr
Clement R. Jones

Chicago, Ill.
Chicago, Ill.
Minneapolis, Minn.
St. Louis, Mo.
Pittsburgh, Pa.

For the Board of Governors

(Term Expiring 1935)

Egerton L. Crispin
Gerald B. Webb
Henry F. Stoll
William Gerry Morgan
Ernest E. Laubaugh
Samuel E. Munson
Robert M. Moore
Thomas Tallman Holt
Roger I. Lee
Adolph Sachs
Allen A. Jones
Leander A. Ruel
Edward J. G. Beardsley
Edwin Bosworth McCready
John O. Manier

(Southern) CALIFORNIA—Los Angeles
COLORADO—Colorado Springs
CONNECTICUT—Hartford
DISTRICT OF COLUMBIA—Washington
IDAHO—Boise
ILLINOIS—Springfield
INDIANA—Indianapolis
KANSAS—Wichita
MASSACHUSETTS—Boston
NEBRASKA—Omaha
(Western) NEW YORK—Buffalo
OKLAHOMA—Oklahoma City
(Eastern) PENNSYLVANIA—Philadelphia
(Western) PENNSYLVANIA—Pittsburgh
TENNESSEE—Nashville

G. C Richards
Jabez Elliott
William M James

UTAH—Salt Lake City
ONTARIO—Toronto, Canada
PANAMA AND THE CANAL ZONE

Lewis B. Flinn
Fred Todd Cadham

(Term Expiring 1934)

DELAWARE—Wilmington
MANITOBA—Winnipeg, Canada

Oliver Clarence Nelson

(Term Expiring 1933)

ARKANSAS—Little Rock

A resolution was regularly adopted, accepting the nominations and electing the nominees
Dr George Morris Piersol, President-Elect, spoke a few words of appreciation for the honor bestowed upon him

The meeting adjourned at 5 35 P. M

E R LOVELAND, Executive Secretary

Dr Hugh S Cumming (Fellow), Washington, D C, U S Public Health Service, has been reappointed and confirmed to the office of Surgeon General for another term of four years

Dr William Gerry Morgan (Fellow), Washington, D C, has been appointed a member of the Council from the District of Columbia of the Southern Medical Association, the reappointment having been announced recently by the President, Dr Lewis J Moorman (Fellow), Oklahoma City, Oklahoma

Dr Joseph Yampolsky (Fellow), Atlanta, Georgia, has been elected First Vice-President of the Fulton County Pediatric Society, for 1932

Dr William Stroud (Fellow), Philadelphia, Pa, professor of cardiology in the Graduate School of the University of Pennsylvania, gave a lecture in the Sunbury High School auditorium, January 19, on "The Presence of Heart Disease in Children"

Dr Paul D White (Fellow), Harvard Medical School, Boston, Mass, gave an address before the Richmond Academy of Medicine on February 9, his subject being "The Treatment of Cardiovascular Disease"

Dr White was also a visitor to the Medical College of Virginia this month, and gave a clinic for third and fourth year medical students

Dr James S McLester (Fellow), Birmingham, Ala, professor of medicine, Univer-

sity of Alabama, delivered the third annual Stuart McGuire Lecture of the Medical College of Virginia, Richmond, on the night of March 4 Dr McLester, a special investigator in the field of nutrition, spoke on "Nutrition in Its Newer Aspects"

Dr Jonathan C Meakins (Fellow), Montreal, Que, Canada, addressed the San Francisco County Medical Society, March 15, on "Treatment of Cardiac Irregularities"

Dr George Piness (Associate), Los Angeles, Calif, addressed the San Diego County Medical Society, March 8, on "Practical Application of Allergy in General Medicine"

Dr Louie M Limbaugh (Fellow), and Dr Thomas M Palmer (Associate), both of Jacksonville, Fla, participated in a symposium on the value of the Mantoux tuberculin reaction in the diagnosis of the childhood type of tuberculosis, held before a recent meeting of the Columbia County Medical Society

Dr William W Graves (Fellow), St Louis, Mo, addressed the Madison County Medical Society, March 4, at Alton on "Practical Basis in the Diagnosis of Neurologic Conditions"

Dr William F Lorenz (Fellow), Madison, Wis, presented a paper before the Chicago Neurological Society, March 17, on "Confessions Obtained During Narcosis"

Dr John H Musser (Fellow), New Orleans, La, addressed the East West Feliciana

Bi-Parish Medical Society in Jackson, February 3, on "Some Facts About Nutrition"

The fifth course of lectures under the William Sidney Thayer and Susan Read Thayer Lectureship in clinical medicine at Johns Hopkins Hospital, was given March 22-23, by Dr Alphonse R Dochez, professor of medicine, Columbia University College of Physicians and Surgeons, New York

Dr George B Eusterman (Fellow), Rochester, Minn, addressed the Wayne County Medical Society, Detroit, March 15, on "Incidence and Nature of Gastric Lesions Masquerading as Benign Disease"

Dr Adolph E Voegelin (Fellow), Detroit, Mich, recently delivered four lectures on cardiology at the Evangelical Deaconess Hospital

Dr Horace W Soper (Fellow), St Louis, Mo, spoke on "Diagnosis of Carcinoma of Colon" at the meeting of the St Louis Medical Society, February 23, 1932

Dr James Alexander Miller (Fellow), New York, was among the speakers at a meeting of the advisory council of the Milbank Memorial Fund, March 16-17. The council met in groups, in which discussions were held on health centers, health education and tuberculosis in children, population studies and public health nursing

Dr Cyrus C Sturgis (Fellow), Ann Arbor, Mich, addressed the Cleveland Academy of Medicine, March 18, on "The Outlook of the Patient with Pernicious Anemia"

Dr Charles W Burr (Fellow), Philadelphia, Pa, contributed to a program dedicated to the memory of Dr Charles K Mills, one of the founders of the Philadelphia Neurological Society, at a meeting of that organization held March 18

The following Fellows appeared on the fourth annual spring clinical conference

sponsored by the Dallas Southern Clinical Society, held at Dallas, March 28-April 2

Dr Thomas R Brown, Baltimore, Md—
"The Story of Digestion and Indigestion",

Dr Samuel A Levine, Boston, Mass—
"Bedside Recognition of Irregularities of the Heart",

Dr Williams McKim Marriott, St Louis, Mo—"Practical Points in the Care and Feeding of Infants"

Dr John E Walker (Fellow), Opelika, Ala, addressed the sixty-fifth annual session of the Medical Association of the State of Alabama, at Mobile, April 19-22. His subject was "Bacteriophage Its Nature and Therapeutic Application"

Dr George T Harding, Jr (Fellow), Columbus, Ohio, spoke before the Muskingum Academy of Medicine, Zanesville, March 2, his subject being "Intoxication Psychoses and Bromides"

Dr Cassius H Hofrichter (Associate), Medina, Wash, addressed the King County Medical Society, Seattle, March 7, on "Tooth Decay, Diet and Vitamins"

Dr Harry R Litchfield (Fellow), Brooklyn, N Y, conducted the Pediatric Pathological Conference at the Cumberland St Hospital of Brooklyn, March 30, 1932. At this conference he contributed a paper on "Congenital Syphilis"

Dr Louis Faugeres Bishop, Jr (Fellow), New York City, presented an example of congenital malformation of the aortic cusps, with detailed report, before the Society for Clinical Study, at its meeting on January 26, 1932

On March 22, 1932, Dr J Reid Broderick (Fellow), of Savannah, Georgia, addressed the Georgia Medical Society in Savannah on the subject, "Coronary Thrombosis and Angina Pectoris"

OBITUARIES

DR ELMER HENDRICKS FUNK

Dr Elmer Hendricks Funk (Fellow), Philadelphia, a much respected and admired clinician of the Quaker City's, so termed, "younger group" and a medical teacher and writer of rare individuality and charm, died suddenly of angina pectoris at his home in Overbrook, Pennsylvania, on May 13, 1932, aged 46 years

He was born, reared and educated in Philadelphia, being an honor graduate of the Jefferson Medical College in 1908, and having subsequently served the Jefferson Medical College Hospital, successively, as Resident Physician, Chief Resident Physician, Medical Director and Medical Director and Physician in Charge of the Department for Diseases of the Chest. He also served as Resident Physician in the Philadelphia Hospital for Contagious Diseases and at the White Haven Sanitarium for Tuberculosis

Dr. Funk inherited a pleasing and gracious personality and possessed a cheerful, unselfish and happy disposition. Early in his medical career the kindly Fates brought him into intimate contact with a select group of vigorous and inspiring personalities for whose names and traits all Philadelphians are justly proud. To mention but three of a much larger number whose wholesome influence would prove a decided stimulus to any medical man, even if he were far less gifted and brilliant in intellect than was Elmer Funk, will suffice. To have enjoyed frequent conferences with such sterling and altruistic characters as the late lamented Judge Meyer Sulzberger and the Hon-

orable William Potter or the, fortunately for Philadelphia and for the Jefferson Medical College and Hospital, still active and enthusiastic Alva B Johnson, was ideal training for a young man's mental and spiritual growth. To work early and intimately, for a period of years, with such excellent physicians as Hobart A Hare, F X Dercum, W M L Coplin, Randle C Rosenberger, J Parsons Schaeffer, Francis Stewart, Albert P. Brubaker, James C Wilson, S Solis-Cohen, Chevalier Jackson, E Quin Thornton, John H Gibbon, J Chalmers Da Costa, Thomas McCrae and similar practical idealists in the profession of medicine, is the traditional kind of training that tends to produce the high type of physician that Elmer Funk became. A little later in his life, fortunate chance brought about a professional intimacy with such inspiring men as Lawrence F Flick, James M Anders, Charles J Hatfield, Henry Page, H R. M Landis, George W. Norris, Arthur Newlin, Eugene Opie and Joseph Walsh. Elmer Funk was a fortunate youth to possess such professional colleagues and friends, and they were equally fortunate to work with such a whole-souled and appreciated junior associate.

Dr Funk became interested in medical teaching and writing even in his undergraduate medical student days, and he later served faithfully, brilliantly and helpfully as Demonstrator, Lecturer, Assistant Professor, Associate Professor and Clinical Professor of Medicine in his Alma Mater.

In September, 1931, Dr Funk was selected by unanimous vote of the

Board of Trustees of the Jefferson Medical College, to succeed the late Hobart A. Hare as Professor of Therapeutics in that century-old institution. Few medical men, in any age, have crowded as much of work, study, investigation, research, teaching, writing, lecturing, work for organized medicine and civic philanthropy as Dr. Funk accomplished in his too brief span of years into their lives.

Dr. Funk had an active part in many organizations and was, perhaps, best known for his intimate knowledge of diseases of the respiratory system. He was assistant editor of the third edition of the "Osler System of Medicine," and in 1930 published a book entitled, "The Diseases of the Respiratory Tract."

His interest in all phases of tuberculosis, and the active part that he played in the campaign against this disease, resulted in his frequently being termed "a tuberculosis specialist."

Dr. Funk became a Fellow of the American College of Physicians on April 1, 1923. At the recent Clinical Session of the College at San Francisco, he was unanimously selected as Treasurer. He was a member of the Council of the Association of American Physicians, for a number of years he had been the Recorder of this Association.

He was an admired and beloved member of the Interurban Medical Association, former President of the Pennsylvania Tuberculosis Association and member and active worker in the Philadelphia Health Council. He was a Distinguished Fellow of the American Association of Physicians of Philadelphia, a Consulting Physician to the Jefferson Hospital, the

Pennsylvania Hospital and White Haven Sanitarium. He was a fluent speaker, a teacher of exceptional talent and ability and a generous contributor of excellent papers to all medical publications. His premature death has robbed the medical profession of a forceful and useful member, and he will long be lovingly remembered by his host of friends and patients.

(Furnished by E. J. G. BEARDSLEY, M.D., F.A.C.P., Governor for Eastern Pennsylvania.)

DR. JAMES BIRNEY GUTHRIE

Dr. James Birney Guthrie (Fellow), the son of J. B. Guthrie and Clara Merrick, was born in New Orleans on January 3, 1876. His maternal grandfather was E. T. Merrick, Sr., Chief Justice of the Supreme Court of Louisiana, and his maternal grandmother was Caroline Merrick, pioneer worker in the ranks of the woman suffrage movement.

After his preliminary education in the public schools of New Orleans he entered Tulane University of Louisiana, from which he received the degrees of bachelor of science in 1896, and of doctor of medicine in 1900. He was the valedictorian of his class in the medical school. He served for two years as an intern at Charity Hospital. Immediately upon his graduation in medicine he was appointed Lecturer and Instructor in Materia Medica and Therapeutics at Tulane University. After four years he was promoted to the position of Associate Professor of Clinical Medicine, and in 1910 he was made Professor of Clinical Medicine, which position he held until 1928. In 1931 he was appointed Professor and Head of the Department of Medicine.

in the new Louisiana State University Medical School. He was serving in this capacity at the time of his death.

Dr Guthrie was one of the first group established in New Orleans to conduct a clinical laboratory, in 1902. He was a pioneer in the field of clinical roentgenology, having set up one of the first x-ray apparatuses in New Orleans. At that time he had only an old static machine and improvised an interrupter of his own. From the time of his entrance into the Charity Hospital as an intern he served that institution uninterruptedly except for the term of his military service. He was a strict disciplinarian and his wards were always most carefully attended. He was the first roentgenologist at Touro Infirmary and when he retired from this field to devote himself entirely to clinical medicine he was named consultant in medicine at that institution. In this capacity he gave 10 years of devoted service to the diabetic clinic. At one time he was chairman of the staff at Hotel Dieu. Entering the army in 1918 as a major, he went overseas and was discharged in the spring of 1919 as lieutenant colonel. Subsequently he attained the rank of colonel in the Medical Reserve Corps.

Dr Guthrie was always active and interested in the work of organized medicine. He was a member of the Orleans Parish Medical Society, Louisiana State Medical Society, American Society of Tropical Medicine, American Medical Association, Association of Military Surgeons. He was elected to fellowship in the American College of Physicians on March 9, 1928. He was president of the Orleans Parish Medical Society in 1928.

Dr Guthrie had been ill for a number of weeks. The cause of his death, on March 8, 1932, was acute pericarditis.

(Furnished by RANDOLPH LYONS, M.D., F.A.C.P., Governor for Louisiana.)

DR WILLIAM CHARLES HEUSSY

Dr William Charles Heussy (Fellow), Seattle, Washington, died March 21, 1932, following an operation for obstruction of the common bile duct, age 62.

Dr Heussy was born in Buffalo, N.Y., attended the public schools there and later graduated from the University of Buffalo School of Medicine in 1895. He did postgraduate work at the Sloan Hospital and the London Hospital, of England, at the University of Edinburgh, at the Rotunda Hospital of Dublin, Ireland, and at the University of Pennsylvania. From 1906 to 1910, he was Lecturer on Hygiene at the Providence Hospital, from 1910 to 1912, President of the Board, Minor Hospital, 1913, Consulting Physician, City Hospital, 1916, Consulting Physician, King County Hospital, and from 1925 until 1928, Chief of the Medical Staff of the Columbus Hospital. He was Vice President of the Staff at this Hospital at the time of his death.

Dr Heussy was a member of the King County Medical Society, Washington State Medical Association, Fellow of the American Medical Association and past President of the Association for the Study of Internal Secretions. He was elected a Fellow of the American College of Physicians in 1917.

Index

- A** BSTRACTS 74, 234, 389, 524, 663, 807, 943, 1041, 1198, 1324, 1440, 1554
- Accidental injuries and occupational diseases Editorial 523
- Acetyl-choline hydrochloride, treatment with peripheral vascular diseases W C Waters 1267
- Adequate treatment of anemia George R Minot and William B Castle 159
- Adrenal cortex, the vital hormones of the F A Hartman, B D Bowen, G W Thorn and C W Greene 539
- Advanced pulmonary tuberculosis Lewis J Moorman 1022
- Agranulocytosis its classification, with cases and comments Stewart R Roberts and Roy R Kracke 40
- Alexander, H L An evaluation of the skin test in allergy 52
- Allen, Edgar V (with Geo E Brown) Raynaud's disease affecting men 1384
- Allen, Edgar V (with L M Waller) The use of sulphur for the production of fever in peripheral vascular disease 478
- Allergy, an evaluation of the skin test in H L Alexander 52
- Amebiasis, complement fixation in diagnosis of C F Craig 170
- American mountain tick-fever and spotted fever of the Rocky Mountains, comparative epidemiography Noxon Toomey 601
- American mountain tick-fever, semeiography and nosology Noxon Toomey 912
- Amoss, Harold L Treatment of recurrent erysipelas 500
- Anderson, J P Quinidine therapy in the treatment of cardiac irregularities due to hyperthyroidism 825
- Andresen, A F R Medical aspects of peptic ulcer 192
- Anemia, adequate treatment of George R Minot and W B Castle 159
- Anemia associated with gastrointestinal disorders, clinical considerations and value of iron in treatment C S Keefer 740
- Anemias, causes, classification and diagnosis of E E Osgood and H D Haskins 1367
- Anemia, diet as a factor in the etiology of Richard A Kern 729
- Anemia, pernicious, the coincidental occurrence of diabetes mellitus and report of two cases Charles Shook-off 1161
- Anemia, pernicious, the treatment of a comparative study of the use of whole liver, liver extract and ventriculin Hugo A Freund and Alvin E Price 1377
- Anemia, pernicious, the treatment of, with dessicated stomach and with liver extract Cyrus C Sturgis and Raphael Isaacs 131
- Anemia, primary aplastic J B Carey and J H Taylor 471
- Aneurysms, dissecting, of the aorta Paul C Samson 117
- Angina pectoris, treatment of, with a tissue vasodilator extract preliminary report Joseph B Wolffe, Donald Findlay and Edward Dessen 625
- Aorta, dissecting aneurysms of the Paul C Samson 117
- Aortitis, syphilitic, a diagnostic triad in C S Danzer 29
- Aortitis, syphilitic, in retrospect William S Middleton 294
- Appendicitis, clinical significance of so-called chronic Julius Friedenwald and Theodore H Morrison 1
- Application of a modified psychiatric approach in the treatment of certain gastrointestinal disorders Theodore H Morrison and Samuel Morrison 371
- Armstrong, Charles Post-vaccination encephalitis 33

- Arsphenamines, toxic granulocytopenia, purpura hemorrhagica and aplastic anemia following the Adolph B Loveman 1238
- Arterial occlusions, multiple H W. Dana 955
- Arthritis, colonic changes in chronic W H Dickson 408
- Arthritis, experimental basis for intravenous vaccine therapy in chronic B J Clawson and M Wetherby 1447
- Arthritis, rheumatoid Russell L Cecil 23
- Arthritis, the relation of the intestinal tract and diet to the treatment of Ralph Pemberton and E G Peirce 1221
- Ascending paralysis resulting from the drinking of "Jamaica Ginger", a clinical study of fifty cases Delbert H Werden 1257
- Aschheim-Zondek test, significance of positive in the male Editorial 660
- Atrophy, acute yellow, cinchophen poisoning a partial explanation for the increasing incidence of Editorial 231
- Auricular flutter and complete heart block, with restoration of sinus rhythm and A-V conduction Leslie T Gager 463
- Auricular paroxysmal tachycardia caused by digitalis Report of a case Arthur F Heyl 858
- Auriculo-ventricular nodal rhythm Carl V Vischer and L L Lane 1010
- Autopsies, how to obtain more D Schuyler Pulford 1315
- B**ALTZ, JAMES I (with J G Mateer) An evaluation of stool vaccines in chronic irritable colon therapy 982
- Balyeat, Ray M (with Herbert J Rinkel) Further studies in allergic migraine, based on a study of two hundred and two consecutive cases 713
- Barach, Alvan L The therapeutic use of oxygen in heart disease 428
- Barker, Lewellys F Malignant thymoma of reticulum-cell type with pressure on the left lung, trachea, esophagus, left phrenic and left recurrent laryngeal nerves and with metastases to the glands of the left side of the neck, importance of biopsy for differential diagnosis of clinical lymphadenopathies 1113
- Barnes, Arlie R Medical and surgical problems associated with coronary sclerosis 873
- Barr, David P (with Howard A Bulger) The relation of the parathyroid glands to calcium metabolism 552
- Barrier, Charles W Tachycardia 829
- Bell, Howard H Obituary 1333
- Benzol poisoning, blood changes in Editorial 803
- Bernstein, Mitchell Subacute bacterial endocarditis following the extraction of teeth 1138
- Bilateral double kidney with duplication of ureters R M Lintz 924
- Blackford, Staige D Pulmonary lesions in human tularemia 1421
- Blake, Francis G Observations on pneumococcus type III pneumonia 673
- Blood changes in benzol poisoning Editorial 803
- Bollman, Jesse L (with Frank C Mann) Experimentally produced lesions of the liver 699
- Boston, Leonard Napoleon Obituary 398
- Bowen, Byron D (with F A Hartman, G W Thorn and C W Greene) The vital hormone of the adrenal cortex 539
- Brain, metastatic malignant tumors of the Harold F Dunlap 1274
- Breuer, Miles J The prestige of the internist 381
- Bronchomoniliasis Otis S Warr 307
- Brown, George E (with Bayard T Horton) Thrombo-angitis obliterans among persons past middle age 613
- Brown, George E (with Edgar V Allen) Raynaud's disease affecting men 1384
- Brown, Thomas R Early diagnosis of neoplasms of the digestive tract 9
- Bulger, Howard A (with D P Barr) The relation of the parathyroid glands to calcium metabolism 552
- Burdock, the effect of the ingestion of, on normal and diabetic individuals—

- a preliminary report A A Silver and John C Krantz 274
- Burgess, Alex M The reaction to nitrates in the anginal syndrome and arterial hypertension 441
- Burnett, Clough T Rheumatic heart disease 1337
- Butler, C S Hero worship and the propagation of fallacies 1033
- C**ALCIUM metabolism, the relation of the parathyroid glands to Harold A Bulger and David P Barr 552
- Cancer, on the "cause" of Editorial 385
- Carbon monoxide deaths Editorial 71
- Carcinomas, including seven primary, in the lung with autopsy findings, Malignancy in the lung Henry Monroe Moses 765
- Cardiac conditions in exophthalmic goiter, the historical development of the present conception of A Morris Ginsberg 505
- Cardiac pain, a theory of the causation of Alexander Lambert 256
- Carey, James B (with J H Taylor) Primary aplastic anemia, a discussion and report of two cases 471
- Castle, W B (with G R Minot) The adequate treatment of anemia 159
- Causes, classification and differential diagnosis of anemias Based on the detailed examination of over 200 patients and a study of the literature Edwin E Osgood and Howard D Haskins 1367
- Cecil, Russell L Rheumatoid arthritis 23
- Chapell, Carl Donald Obituary 1220
- Chapman, Lawrence Evans Obituary 953
- Chests, observations on contour of normal and tuberculous female S A Weisman 907
- (3) Cholelithiasis, unusual case of Laboratory methods in clinical medicine Report of three cases (1) Diaphragmatic eventration, (2) Chronic nephritis without hypertension, cardiac hypertrophy, or retinal changes Samuel Levine 1000
- Chondrodysplasia, hereditary deforming M A Spangelberger 962
- Choroidal tubercles, the clinical significance of R T Paton 997
- Christian, Henry A Chronic myocardial insufficiency and its therapeutic management 95
- Chronic myocardial insufficiency and its therapeutic management Henry A Christian 95
- Cinchophen poisoning a partial explanation for the increasing incidence of acute yellow atrophy Editorial 231
- Circulatory adjustments in heart disease Soma Weiss 100
- Cirrhosis, portal, clinical aspects of Albert M Snell 338
- Civic pride and public health Editorial 1553
- Clapp, C A Modern conception of retinal detachment with its relation to internal medicine 1313
- Clark, Malhe Adkin Obituary 1333
- Clawson, B J (with M Wetherby) An experimental basis for intravenous vaccine therapy in chronic arthritis with a summary of results obtained in patients 1447
- Clinical aspects of portal cirrhosis Albert M Snell 338
- Clinical significance of choroidal tubercles R T Paton 997
- Clinical significance of so-called chronic appendicitis Julius Friedenwald and Theodore H Morrison 1
- Coincidental occurrence of diabetes mellitus and pernicious anemia report of two cases Charles Shook-off 1161
- Colds, etiology of J E Walker 1526
- College News Notes 80, 238, 393, 530, 668, 813, 948, 1045, 1203 1329 1445 1560
- Collins, Harry A Ephedrine in the treatment of narcolepsy 1289
- Colonic changes in chronic arthritis W H Dickson 408
- Comparative study of the use of whole liver, liver extract and ventriculin Hugo A Freund and Alvin E Price 1377
- Complement fixation in the diagnosis of amebiasis Charles F Craig 170
- Control of the tick-borne diseases, methods and economics Noxon Toomey 1513

- Cooper, George F Post-pneumonic lung abscess resembling lung tumor, with case report 1308
- Corbus, Burton R Editorial, Medicine to-day and to-morrow 1196
- Coronary sclerosis, medical and surgical problems associated with Arlie R Barnes 873
- Coronary thrombosis, the management of, and its complications Blanton P Seward 1145
- Craig, C F Complement fixation in diagnosis of amebiasis 170
- Crawford, J Hamilton (with Louis H Sigler and H Fruchter) Paroxysmal tachycardia related to the menstrual period 1155
- Cutaneous manifestations of systemic diseases Udo J Wile 1103
- D**ANA, HAROLD W Multiple arterial occlusions 955
- Danzer, C S A diagnostic triad in syphilitic aortitis 29
- Davis, Adam Clarke Obituary 1047
- Denman, Harold C Syphilis of the lung, report of case with autopsy findings 895
- Dercum, Francis Xavier Obituary 92
- Dessen, Edward (with J B Wolffe and D Findlay) Treatment of angina pectoris with a tissue vasodilator extract 625
- Diabetes, hypertension and H J John 1462
- Diabetes insipidus, the etiology and treatment of T. B Futcher 566
- Diabetes in the negro race E J Leopold 285
- Diabetes mellitus and pernicious anemia, the coincidental occurrence of Charles Shookoff 1161
- Diabetes mellitus, fallacy of the weighed diet in the treatment of Helmuth Ulrich 1487
- Diabetes mellitus, the insulin coefficient, an improved method for the clinical control of John R Williams 264
- Diabetic, does liver therapy benefit the E L Sevringhaus 1387
- Diabetic individuals, the effect of the ingestion of burdock on normal and A A Silver and John C Krantz 274
- Diagnosis of hyperthyroidism Maynard E Holmes 1028
- Diagnostic triad in syphilitic aortitis C S Danzer 29
- Diagnostic value of secretory function in gastric disease various methods studied and compared Ernest H Gaither 992
- Diaphragm, on the morbid anatomy of Baldwin Lucké 750
- Diaphragm, the heart and the I M Trace 759
- (1) Diaphragmatic eventration, laboratory methods in clinical medicine Report of three cases, (2) Chronic nephritis without hypertension, cardiac hypertrophy, or retinal changes, (3) Unusual case of cholelithiasis Samuel Levine 1000
- Dickson, W H Colonic changes in chronic arthritis 408
- Diet as a factor in the etiology of anemia Richard A Kern 729
- Dietetic control of some forms of hypertension and the associated gastrointestinal and nervous symptoms V C Rowland 971
- Dietetic treatment of tuberculosis Ernest S Mariette 793
- Digestive tract, early diagnosis of neoplasms of the Thomas R Brown 9
- Disease, gastric, diagnostic value of secretory function in various methods studied and compared Ernest H Gaither 992
- Dissecting aneurysms of the aorta Paul C Samson 117
- Does liver therapy benefit the diabetic? Elmer L Sevringhaus 1387
- Douglas, Robert Gibbs Obituary 672
- Dunlap, Harold F Metastatic malignant tumors of the brain 1274
- Dysplasia, hereditary ectodermal, of the anhidrotic type William H Gordon and Robert C Jameson 358
- E**ARLY diagnosis of neoplasms of the digestive tract Thomas R Brown 9
- Early manifestations of rheumatic infections in young children C C McLean 1357
- Edgerly, Edward Tyler Obituary 951

- Editorials 70, 231, 385, 518, 659, 803, 932, 1039, 1196, 1321, 1437, 1552
- Effect of the ingestion of burdock on normal and diabetic individuals—a preliminary report A A Silver and John C Krantz 274
- Electrocardiographic studies of the effects of propylene as a general anesthetic in man Morris H Kahn and Lloyd K Riggs 651
- Emerson, Haven The influence of the practitioner of medicine in guiding the public towards health 57
- Encephalitis, post-vaccination Charles Armstrong 333
- Endocarditis, gonorrheal Arthur H Hoffman and Floyd C Taggart 1397
- Endocarditis, subacute bacterial, following the extraction of teeth M Bernstein 1138
- Ephedrine in the treatment of narcolepsy Harry A Collins 1289
- Erysipelas, treatment of recurrent Harold L Amoss 500
- Etiology and treatment of diabetes insipidus T B Futcher 566
- Etiology of colds John E Walker 1526
- Eustis, Allan The response of the cardiovascular system to respiratory strain A measure of myocardial efficiency 842
- Evaluation of stool vaccines in chronic irritable colon therapy John G Mateer and James I Baltz 982
- Evaluation of the skin test in allergy H L Alexander 52
- Evans, Frank A The level of oxygen exchange in obesity as a factor in planning treatment 574
- Exophthalmic goiter, fallacies and dangers in treatment of, by iodine W O Thompson and P K Thompson 1129
- Experimental basis for intravenous vaccine therapy in chronic arthritis B J Clawson and M Wetherby 1447
- Experimentally produced lesions of the liver Jesse L Bollman and Frank C Mann 699
- FALLACIES and dangers in the treatment of exophthalmic goiter by iodine Willard Owen Thompson and Phebe K Thompson 1129
- Fallacy of the weighed diet in the treatment of diabetes mellitus Helmut Ulrich 1487
- Findlay, Donald (with J B Wolffe and Edward Dessen) Treatment of angina pectoris with a tissue vasodilator extract 625
- Fluoride, mottled enamel due to Editorial 1321
- Follansbee, G E The profession and the public 224
- Frazer, Thompson Obituary 954
- Fremmel, Frank (with Karl J Henrichsen and Henry C Sweany) Pulmonary infections by Friedlander's bacillus 886
- Freund, Hugo A (with Alvin E Price) A comparative study of the use of whole liver, liver extract and ventriculin 1377
- Friedenwald, Julius (with Theodore H Morrison) The clinical significance of so-called chronic appendicitis 1
- Friedlander's bacillus (*Bacillus Mucosus Capsulatus*), pulmonary infections by the Frank Fremmel, Karl J Henrichsen and Henry C Sweany 886
- Fruchter, H (with J H Crawford and L H Sigler) Paroxysmal tachycardia related to the menstrual period 1155
- Funk, Elmer Hendricks Obituary 1576
- Further studies in allergic migraine, based on a series of two hundred and two consecutive cases Ray M Balyeat and Herbert J Rinkel 713
- Futcher, T B The etiology and treatment of diabetes insipidus 566
- GAGER, LESLIE T Auricular flutter and complete heart block, with restoration of sinus rhythm and A-V conduction 463
- Gaither, Ernest H Diagnostic value of secretory function in gastric disease various methods studied and compared 992
- Gastric disease, diagnostic value of secretory function in various methods studied and compared Ernest H Gaither 992
- General practitioner and the public health program Felix J Underwood 65

- Ginsberg, A Morris The historical development of the present conception of cardiac conditions in exophthalmic goiter 505
- Goiter, exophthalmic, the historical development of the present conception of cardiac conditions in A Morris Ginsberg 505
- Goiter, pathological classification of W Carpenter MacCarty 178
- Goldsmith, Oliver, M D Louis H Roddis 1427
- Gonorrheal endocarditis Summary of the literature and report of a case Arthur M Hoffman and Floyd C Taggart 1397
- Gordon, William H (with Robert C Jamieson) Hereditary ectodermal dysplasia of the anhidrotic type 358
- Gotten, H B Myxedema 1492
- Granulocytopenia, toxic, purpura hemorrhagica and aplastic anemia following the use of the arsphenamines A B Loveman 1238
- Greene, Clayton W (with F A Hartman, B D Bowen and G W Thorn) The vital hormone in adrenal cortex 539
- Guthrie, James Birney Obituary 1577
- H**AFT, HENRY H The use of histamin HCl as a test meal 1175
- Hale, Raleigh Peter Obituary 1047
- Hall, Harry M Obituary 246
- Hartman, Frank A (with B D Bowen, G W Thorn and C W Greene) The vital hormone of the adrenal cortex 539
- Hartman, H R (with D L Wilbur) Malignant melanoma with delayed metastatic growths 201
- Haskins, Howard D (with E E Osgood) Causes, classification and differential diagnosis of anemias 1367
- Heart and the diaphragm I M Trace 759
- Heart disease, circulatory adjustments in Soma Weiss 100
- Heart disease, rheumatic a review Clough Turrill Burnett 1337
- Heart disease, the therapeutic use of oxygen in Alvan L Barach 428
- Heart in hyperthyroidism Henry M Thomas, Jr 184
- Hein, Theodore Leacraft Obituary 824
- Henrichsen, Karl J (with Frank Fremmel and Henry C Sweany) Pulmonary infections by Friedlander's bacillus 886
- Hereditary deforming chondrodysplasia Case report M A Spangelberger 962
- Hereditary ectodermal dysplasia of the anhidrotic type William H Gordon and Robert C Jamieson 358
- Heredity of elliptical erythrocytes (Ovalocytosis) Editorial 659
- Hero worship and the propagation of fallacies C S Butler 1033
- Heussy, William Charles Obituary 1578
- Heyl, Arthur F Auricular paroxysmal tachycardia caused by digitalis 858
- Himmelberger, L R The significance of lymphatic tissue and adenoma-like areas in the thyroid gland 1404
- Histamin HCl as a test meal H H Haft 1175
- Historical development of the present conception of cardiac conditions, in exophthalmic goiter A Morris Ginsberg 505
- Hodgkin's disease, the nature and etiology of Editorial 1437
- Hoffman, Arthur M (with F C Taggart) Gonorrheal endocarditis 1397
- Hollingsworth, E W Ventricular paroxysmal tachycardia 1506
- Holmes, Maynard E The diagnosis of hyperthyroidism 1028
- Horton, Bayard T (with Geo E Brown) Thrombo-angitis obliterans among persons past middle age 613
- Hospital, the, its relation to the community and to the medical profession Winford H Smith 212
- How to obtain more autopsies D Schuyler Pulford 1315
- Hypertension and diabetes H J John 1462
- Hypertension, the dietetic control of some forms of V C Rowland 971
- Hyperthyroidism, quimidine therapy in the treatment of cardiac irregularities due to J P Anderson 825
- Hyperthyroidism, the diagnosis of Maynard E Holmes 1028

- Hyperthyroidism, the heart in H M Thomas, Jr 184
- Hyperthyroidism, the management of severe and atypical Frank H Lahey 1123
- Hypothyroidism without myxedema J B Youmans and S S Riven 1497
- I**NFLUENCE of the practitioner of medicine in guiding the public towards health Haven Emerson 57
- Insulin coefficient J R Williams 264
- Internal radiation in the causation of malignancy Editorial 932
- Isaacs, Raphael (with C C Sturgis) The treatment of pernicious anemia with desiccated stomach and with liver extract 131
- J**AMAICA JINGER," ascending paralysis resulting from the drinking of a clinical study of fifty cases Delbert H Werden 1257
- Jamieson, R C (with W H Gordon) Hereditary ectodermal dysplasia of the anhidrotic type 358
- Jenks, Horace Howard Obituary 245
- John, H J Hypertension and diabetes 1462
- John Phillips memorial prize Editorial 1039
- K**AHN, MORRIS H (with Lloyd K Riggs) Electrocardiographic studies of the effects of propylene as a general anesthetic in man 651
- Katznelbogen, S Somatic disorders of functional origin 1017
- Katznelbogen, S The significance of meningeal permeability 1168
- Keefer, Chester S Anemia associated with gastrointestinal disorders, clinical considerations and value of iron in treatment 740
- Kern, Richard A Diet as a factor in the etiology of anemia 729
- Kerr, William J San Francisco as a medical center 1178
- Kidney, bilateral double, with duplication of ureters Robert M Lintz 924
- Kracke, Roy R (with Stewart R Roberts) Agranulocytosis its classification with cases and comments 40
- Krantz, J C (with A A Silver) The effect of ingestion of burdock on normal and diabetic individuals 274
- L**ABORATORY methods in clinical medicine Report of three cases (1) Diaphragmatic eventration, (2) Chronic nephritis without hypertension, cardiac hypertrophy or retinal changes, (3) Unusual case of cholelithiasis Samuel Levine 1000
- Lahey, Frank H The management of severe and of atypical hyperthyroidism 1123
- Lambert, Alexander A theory of the causation of cardiac pain 256
- Lane, Lowell L (with Carl V Vischer) Auriculoventricular nodal rhythm with report of cases 1010
- Layman considers migraine Walter B Sheppard 1532
- Leopold, Eugene J Diabetes in the negro race 285
- Level of oxygen exchange in obesity as a factor in planning treatment Frank A Evans 574
- Levine, Samuel Laboratory methods in clinical medicine Report of three cases (1) diaphragmatic eventration, (2) chronic nephritis without hypertension, cardiac hypertrophy or retinal changes, (3) unusual case of cholelithiasis 1000
- Lintz, Robert M Bilateral double kidney with duplication of ureters 924
- Liver, experimentally produced lesions of Jesse L Bollman and Frank C Mann 699
- Liver, use of whole, liver extract and ventriculin H A Freund and A E Price 1377
- Longcope, Warfield T Variations in manifestations of rheumatic fever in relation to climate 401
- Loveland, Bradford Churchill Obituary 824
- Loveman, Adolph B Toxic granulocytopenia, purpura hemorrhagica and aplastic anemia following the arsphenamines 1238
- Lucke, Baldum On the morbid anatomy of the diaphragm 750

- Lung abscess, post-pneumonic, resembling lung tumor G F Cooper 1308
- Lung, malignancy in the, including seven primary carcinomas in the lung H M Moses 765
- Lung, syphilis of the, report of a case with autopsy findings Harold Comonfort Denman 895
- Lymphoid tissue changes in the prodromal stage of measles Editorial 1039
- M**ACCARTY, W C Pathological classification of goiter 178
- MacLachlan, W W G (with H H Permar) Tularemic pneumonia 687
- Malaria, spontaneous rupture of the spleen in inoculation Editorial 72
- Malignancy in the lung, including seven primary carcinomas in the lung with autopsy findings Henry Monroe Moses 765
- Malignancy, internal radiation in the causation of Editorial 932
- Malignant melanoma with delayed metastatic growths D L Wilbur and H R Hartman 201
- Malignant thymoma of reticulum-cell type with pressure on the left lung, trachea, esophagus, left phrenic and left recurrent laryngeal nerves, and with metastases to the glands of the left side of the neck, importance of biopsy for differential diagnosis of cervical lymphadenopathies Lewellys F Barker 1113
- Malignant tumors, metastatic, of the brain H F Dunlap 1274
- Mallory, T B (with J H Means) Total occlusion of the right branch of the pulmonary artery by an organized thrombus 417
- Management of coronary thrombosis and its complications Blanton P Seward 1145
- Management of severe and of atypical hyperthyroidism Frank H Lahey 1123
- Mann, Frank C (with Jesse L Bollman) Experimentally produced lesions of the liver 699
- Many sided question of protein in nephritis W S McCann 579
- Mariette, Ernest S The dietetic treatment of tuberculosis 793
- Mateer, John G (with J I Baltz) An evaluation of stool vaccines in chronic irritable colon therapy 982
- McCann, W S The many sided question of protein in nephritis 579
- McLean, C C Early manifestations of rheumatic infections in young children 1357
- Meagher, John Francis Wallace Obituary 952
- Means, J H (with T B Mallory) Total occlusion of the right branch of the pulmonary artery by an organized thrombus 417
- Measles, the lymphoid tissue changes in the prodromal stage of Editorial 1039
- Mediastinal displacement in pneumothorax W C Pollock 486
- Medical and surgical problems associated with coronary sclerosis Arlie R Barnes 873
- Medical aspects of peptic ulcer Albert F R Andresen 192
- Medicine to-day and to-morrow Editorial B R Corbus 1196
- Medulloblastoma cerebelli Karl Rothschild 643
- Melanoma, malignant, with delayed metastatic growths D L Wilbur and H R Hartman 201
- Meningeal permeability, the significance of. S Katzenelbogen 1168
- Metastatic malignant tumors of the brain Harold F Dunlap 1274
- Middleton, Wm S Syphilitic aortitis in retrospect 294
- Migraine, a layman considers W B Sheppard 1532
- Migraine, allergic, further studies in Ray M Balyeat and H J Rinkel 713
- Minot, Geo R (with Wm B Castle) The adequate treatment of anemia 159
- Modern conception of retinal detachment with its relation to internal medicine C A Clapp 1313
- Moorman, Lewis J Advanced pulmonary tuberculosis 1022
- Morrison, Samuel (with Theodore H Morrison) The application of a modified psychiatric approach in the treatment of certain gastrointestinal disorders 371
- Morrison, Theodore H (with Samuel Morrison) The application of a

- modified psychiatric approach in the treatment of certain gastrointestinal disorders 371
- Morrison, Theodore H (with Julius Friedenwald) The clinical significance of so-called chronic appendicitis 1
- Mortality rate for the first months of 1931 Editorial 233
- Moses, Henry Monroe Malignancy in the lung, including seven primary carcinomas in the lung with autopsy findings 765
- Mottled enamel due to fluoride Editorial 1321
- Mountain fever and spotted fever of the Rocky Mountains, clinical studies Noxon Toomey 585
- Mountain, Rocky, spotted fever type, typhus-like (spotted) fever from tick-bite, identified with a symbiont Proteus-like septicemia Noxon Toomey 1296
- Multiple arterial occlusions Harold W Dana 955
- Murray, Leonard M Obituary 535
- Myocardial insufficiency, chronic, and its therapeutic management Henry A Christian 95
- Myxedema H B Gotten 1492
- N**ARCOLEPSY, ephedrine in the treatment of H A Collins 1289
- Nature and etiology of Hodgkin's disease Editorial 1437
- Negro race, diabetes in the Eugene J Leopold 285
- Neoplasms of the digestive tract, early diagnosis of Thos R Brown 9
- (2) Nephritis, chronic, without hypertension, cardiac hypertrophy or retinal change, Laboratory methods in clinical medicine Report of three cases (1) Diaphragmatic eventration, (3) Unusual case of cholelithiasis Samuel Levine 1000
- Nephritis, the question of protein in W S McCann 579
- Nitrites, the reaction to, in the anginal syndrome and arterial hypertension Alex M Burgess 441
- O**BESITY, the level of oxygen exchange in, as a factor in planning treatment F A Evans 574
- O**BITUARIES
- Howard H Bell 1333
- Leonard Napoleon Boston 398
- Carl Donald Chapell 1220
- Lawrence Evans Chapman 953
- Malhe Adkin Clark 1333
- Adam Clarke Davis 1047
- Francis Xavier Dercum 92
- Robert Gibbs Douglas 672
- Edward Tyler Edgerly 951
- Thompson Frazer 954
- Elmer Hendricks Funk 1576
- James Birney Guthrie 1577
- Raleigh Peter Hale 1047
- Harry M Hall 246
- Theodore Leacraft Hem 824
- William Charles Heussy 1578
- Horace Howard Jenks 245
- Bradford Churchill Loveland 824
- John Francis Wallace Meagher 952
- Leonard M Murray 535
- Edward P Schatzman 538
- James P Schureman 399
- Arthur Clifford Selmon 244
- William Stephens Shields 537
- Elmore Callaway Thrash 536
- Reynold Webb Wilcox 244
- Hugh Spaulding Willson 1332
- Henry Lyle Winter 537
- Joseph Witham Young 538
- Observations on pneumococcus type III pneumonia Francis G Blake 673
- Observations on rheumatic pancarditis and infective endocarditis W S Thayer 247
- Observations on the contour of normal and tuberculous female chests S A Weisman 907
- Occlusion, total, of the right branch of the pulmonary artery by an organized thrombus J H Means and T B Mallory 417
- On the morbid anatomy of the diaphragm Balduin Lucke 750
- Osgood, Edwin E (with H D Haskins) Causes, classification and differential diagnosis of anemias 1367
- Ovalocytosis, heredity of elliptical erythrocytes Editorial 659
- Oxygen, therapeutic use of, in heart disease Alvan L Barach 428
- P**AIN, cardiac, a theory of the causation of Alexander Lambert 256

- Pancarditis, rheumatic, observations on, and infective endocarditis W S Thayer 247
- Paralysis, ascending, from "Jamaica Ginger" D H Werden 1257
- Parathyroid glands, the relation of, to calcium metabolism H A Bulger and D P Barr 552
- Paroxysmal tachycardia related to the menstrual period J Hamilton Crawford, Louis H Sigler and H Fruchter 1155
- Pathological classification of goiter W Carpenter MacCarty 178
- Paton, R T The clinical significance of choroidal tubercles 997
- Paul, W D (with F M Smith) Studies on the mechanism of the pain of peptic ulcer 14
- Peirce, E G (with Ralph Pemberton) The relation of the intestinal tract and diet to treatment of arthritis 1221
- Pemberton, Ralph (with E G Peirce) The relation of the intestinal tract and diet to the treatment of arthritis 1221
- Peptic ulcer, medical aspects of A F R Andresen 192
- Peptic ulcer, studies on the mechanism of pain of Fred M Smith and W D Paul 14
- Peripheral vascular diseases, treatment of, with acetyl-choline hydrochloride W C Waters 1267
- Permar, H H (with W W G Mac-lachlan) Tularemic pneumonia 687
- Pernicious anemia, treatment of, with desiccated stomach and with liver extract C C Sturgis and R Isaacs 131
- Phinzy, Thomas B (with E R Pund) Primary sclerosis of pulmonary artery 1391
- Pneumococcus type III pneumonia Francis G Blake 673
- Pneumonia, tularemic H H Permar and W W G Mac-lachlan 687
- Pneumothorax, mediastinal displacement in W C Pollock 486
- Policies, editorial 70
- Pollock, W C Mediastinal displacement in pneumothorax 486
- Portal cirrhosis, clinical aspects of Albert M Snell 338
- Post-pneumonic lung abscess resembling lung tumor, with case report George F Cooper 1308
- Post-vaccination encephalitis Charles Armstrong 333
- Presidential address S Marx White 1540
- Prestige of the internist Miles J Breuer 381
- Price, Alvin E (with H A Freund) Use of whole liver, liver extract and ventriculin 1337
- Primary aplastic anemia, a discussion and report of two cases James B Carey and Joseph H Taylor 471
- Primary sclerosis of the pulmonary artery Report of a case Edgar R Pund and Thomas B Phinzy 1391
- Profession and the public George Edward Follansbee 224
- Program for the general sessions of the sixteenth annual clinical session in San Francisco Editorial, S Marx White 518
- Program of the San Francisco meeting 1048
- Program of the San Francisco meeting Editorial 1040
- Propylene, electrocardiographic studies of the effects of, as a general anesthetic in man Morris H Kahn and Lloyd K Riggs 651
- Pulford, D Schuyler How to obtain more autopsies 1315
- Pulmonary artery, primary sclerosis of the report of a case Edgar R Pund and Thomas B Phinzy 1391
- Pulmonary artery, total occlusion of the right branch of the, by an organized thrombus J H Means and T B Mallory 417
- Pulmonary infections by the Friedlander's bacillus (*Bacillus mucosus capsulatus*) Frank Fremmel, Karl J Henrichsen and Henry C Sweany 886
- Pulmonary lesions in human tularemia, pathological review and report of a fatal case Staige D Blackford 1421
- Pund, Edgar R (with Thomas B Phinzy) Primary sclerosis of the pulmonary artery 1391
- QUINIDINE therapy in treatment of cardiac irregularities due to hyperthyroidism J P Anderson 825

- RADIATION**, internal, in the
causation of malignancy Editorial
ial 932
- Raynaud's disease affecting men
Edgar V Allen and George E Brown 1384
- Reaction to nitrites in the anginal
syndrome and arterial hypertension
Alex M Burgess 441
- Relation of the intestinal tract and diet
to the treatment of arthritis Ralph
Pemberton and E G Peirce 1221
- Relation of the parathyroid glands to
calcium metabolism Harold A
Bulger and David P Barr 552
- Respiratory strain, response of the
cardiovascular system to Allan
Eustis 842
- Response of the cardiovascular system
to respiratory strain a measure of
myocardial efficiency Allan Eustis 842
- Retinal detachment, modern conception
of, with its relation to internal medi-
cine C A Clapp 1313
- Reviews 77, 236, 391, 526,
665, 809, 945, 1043, 1200, 1326, 1442, 1557
- Rheumatic fever, variations in mani-
festations of, in relation to climate
Warfield T Longcope 401
- Rheumatic heart disease C T
Burnett 1337
- Rheumatic infections in young child-
ren C C McLean 1357
- Rheumatic pancarditis and infective
endocarditis W S Thayer 247
- Rheumatoid arthritis Russell L
Cecil 23
- Riggs, Lloyd K (with Morris H
Kahn) Electrocardiographic studies
of the effects of propylene as a gen-
eral anesthetic in man 651
- Rinkel, Herbert J (with Ray M
Balyeat) Allergic migraine 713
- Riven, S S (with J B Youmans)
Hypothyroidism without myxedema 1497
- Roberts, Stewart R (with R R
Kracke) Agranulocytosis its
classification with cases and com-
ments 40
- Roddis, Louis H Oliver Goldsmith,
M D 1427
- Rothschild, Karl Medulloblastoma
cerebelli 643
- Rowland, V C The dietetic control
of some forms of hypertension and
the associated gastrointestinal and
nervous symptoms 971
- SAFETY FIRST** Editorial 804
- Samson, Paul C Dissecting aneu-
rysms of the aorta 117
- San Francisco as a medical center
William J Kerr 1178
- San Francisco session of the American
College of Physicians Editorial 1552
- San Francisco, the city by the Golden
Gate 935
- Saskatchewan experiment Editorial 521
- Schatzman, Edward P Obituary 538
- Schureman, James P Obituary 399
- Sclerosis, primary, of pulmonary
artery E R Pund and T B
Phimzy 1391
- Selmon, Arthur Clifford Obituary 244
- Sevringhaus, Elmer L Does liver
therapy benefit the diabetic? 1387
- Seward, Blanton P The management
of coronary thrombosis and its com-
plications 1145
- Sheppard, W B A layman considers
migraine 1532
- Shields, William Stephens Obituary 537
- Shookoff, Charles The coincidental
occurrence of diabetes mellitus and
pernicious anemia with report of two
cases 1161
- Sigler, Louis H (with J H Crawford
and H Fruchter) Paroxysmal
tachycardia related to the menstrual
period 1155
- Significance of lymphatic tissue and
adenoma-like areas in the thyroid
gland L R Himmelberger 1404
- Significance of meningeal permeability
S Katzenelbogen 1168
- Significance of positive Aschheim-
Zondek test in the male Editorial 660
- Silver, A A (with J C Krantz)
Effect of the ingestion of burdock on
normal and diabetic individuals 274
- Smith, Fred M (with W D Paul)
Mechanism of pain of peptic ulcer 14
- Smith, W H The hospital, its rela-
tion to the community and the medical
profession 212
- Snell, Albert M Clinical aspects of
portal cirrhosis 338

- Somatic disorders of functional origin
S Katzenelbogen 1017
- Spangelberger, M A Hereditary de-
forming chondrodysplasia 962
- Spleen, spontaneous rupture of, in in-
oculation malaria Editorial 72
- Spontaneous rupture of the spleen in in-
oculation malaria Editorial 72
- Spotted fever, and American mountain
tick-fever, of the Rocky Mountains—
comparative epidemiography Noxon
Toomey 601
- Spotted fever and mountain fever of the
Rocky Mountains—clinical studies
Noxon Toomey 585
- Spotted fever, typhus-like, from tick
bite Noxon Toomey 1296
- Standardization of American special-
ists Editorial, G A Pemberton
Wright 805
- Stool vaccines, evaluation of, in chronic
irritable colon therapy J G Mateer
and J I Baltz 982
- Studies on the mechanism of the pain
of peptic ulcer Fred M Smith and
W D Paul 14
- Sturgis, Cyrus C (with R Isaacs)
Treatment of pernicious anemia with
desiccated stomach and with liver ex-
tract 131
- Subacute bacterial endocarditis follow-
ing the extraction of teeth report
of a case Mitchell Bernstein 1138
- Suicides in the United States in 1930
Editorial 232
- Sulphur, the use of, for the production
of fever in peripheral vascular dis-
ease L M Waller and E V Allen 478
- Sweany, Henry C (with Frank Frem-
mel and Karl J Henrichsen)
Pulmonary infections with Fried-
lander's bacillus 886
- Syphilis of the lung Harold Comon-
fort Denman 895
- Syphilitic aortitis, a diagnostic triad in
C S Danzer 29
- Syphilitic aortitis in retrospect W
S Middleton 294
- TACHYCARDIA** Charles W
Barrier 829
- Tachycardia, auricular paroxysmal,
caused by digitalis report of a case
Arthur F Heyl 858
- Tachycardia, paroxysmal, related to the
menstrual period J Hamilton
Crawford, Louis H Sigler, and H
Fruchter 1155
- Tachycardia, ventricular paroxysmal,
with report of a case Edward W
Hollingsworth 1506
- Taggart, Floyd C (with A M Hoff-
man) Gonorrheal endocarditis 1397
- Taylor, Joseph H (with James B
Carev) Primary aplastic anemia,
a discussion and report of two cases 471
- Thayer, W S Observations on rheu-
matic pancarditis and infective en-
docarditis 247
- Theory of the causation of cardiac pain
Alexander Lambert 256
- Therapeutic use of oxygen in heart
disease Alvan L Barach 428
- Thomas, H M, Jr Heart in hyper-
thyroidism 184
- Thompson, Phebe K (with W O
Thompson) Fallacies and dangers
in the treatment of exophthalmic
goiter by iodine 1129
- Thompson, Willard Owen (with Phebe
K Thompson) Fallacies and
dangers in the treatment of exoph-
thalmic goiter by iodine 1129
- Thorn, George W (with F A Hart-
man, B D Bowen and C W
Greene) The vital hormone of the
adrenal cortex 539
- Thrash, Elmore Callaway Obituary 536
- Thrombo-angitis obliterans among per-
sons past middle age Bayard T
Horton and George E Brown 613
- Thymoma, malignant, of the reticulum-
cell type Lewellys F Barker 1113
- Thyroid gland, significance of lymph-
atic tissue and adenoma-like areas in
L R Himmelberger 1404
- Tick-borne diseases, control of, method
and economics Noxon Toomey 1513
- Toomey, Noxon American mountain
tick-fever and spotted fever of the
Rocky Mountains—comparative epi-
demography 601
- Toomey, Noxon American mountain
tick-fever—semeiology and nosol-
ogy 912
- Toomey, Noxon Control of tick-borne
diseases 1513

- Toomey, Noxon Mountain fever and spotted fever of the Rocky Mountains clinical studies 585
- Toomey, Noxon Typhus-like (spotted) fever from tick-bite 1296
- Total occlusion of the right branch of the pulmonary artery by an organized thrombus J H Means and T B Mallory 417
- Toxic granulocytopenia, purpura hemorrhagica and aplastic anemia following the arsphenamines Adolph B Loveman 1238
- Trace, I M The heart and the diaphragm 759
- Treatment of angina pectoris with a tissue vasodilator extract preliminary report Joseph B Wolffe, Donald Findlay and Edward Dessen 625
- Treatment of pernicious anemia with desiccated stomach and with liver extract Cyrus C Sturgis and Raphael Isaacs 131
- Treatment of recurrent erysipelas Harold L Amoss 500
- Tuberculosis, advanced pulmonary Lewis J Moorman 1022
- Tuberculosis, the dietetic treatment of Ernest S Mariette 793
- Tularemia, pulmonary lesions in human Staige D Blackford 1421
- Tularemia pneumonia H H Permar and W W G MacLachlan 687
- Typhus-like (spotted) fever from tick-bite, Rocky Mountain spotted fever type, identified with a symbiont Proteus-like septicemia Noxon Toomey 1296
- ULCER, peptic, medical aspects of Albert F R Andresen 192
- Ulcer, peptic, studies on the mechanism of the pain of Fred M Smith and W D Paul 14
- Ulrich, Helmuth The fallacy of the weighted diet in treatment of diabetes mellitus 1487
- Underwood, Felix J The general practitioner and the public health program 65
- Ureters, bilateral double kidney with duplication of Robert M Lintz 924
- Use of histamin HCl as a test meal Henry H Haft 1175
- Use of sulphur for the production of fever in peripheral vascular disease Lorenz M Waller and Edgar V Allen 478
- VARIATIONS in manifestations of rheumatic fever in relation to climate Warfield T Longcope 401
- Ventricular paroxysmal tachycardia Edward W Hollingsworth 1506
- Vischer, Carl V (with Lowell L Lane) Auriculo-ventricular nodal rhythm with report of cases 1010
- Vital hormone of the adrenal cortex Frank A Hartman, Byron D Bowen, George W Thorn and Clayton W Greene 539
- WALKER, J E Etiology of colds 1526
- Waller, L M (with E V Allen) The use of sulphur for the production of fever in peripheral vascular disease 478
- Warr, Otis S Bronchomoniliasis a clinical and pathological study with report of illustrative cases 307
- Waters, W C Peripheral vascular diseases Treatment with acetylcholine hydrochloride 1267
- Weisman, S A Observations on the contour of normal and tuberculous female chests 907
- Weiss, Soma Circulatory adjustments in heart disease 100
- Weller, Carl Vernon Editorials, abstracts and reviews 70, 231, 385, 659, 803, 932, 1039, 1196, 1321, 1437, 1552
- Werden, D H Ascending paralysis resulting from the drinking of "Jamaica Ginger" a clinical study of fifty cases 1257
- Wetherby, M (with B J Clawson) An experimental basis for intravenous vaccine therapy in chronic arthritis with a summary of results obtained in patients 1447
- White, S Marx Presidential address 1540
- White, S Marx Program for the general sessions of the sixteenth annual clinical session in San Francisco Editorial 518

Wilbur, D L (with H R Hartman)			
Malignant melanoma with delayed metastatic growths	201	lay and Edward Dessen) Treatment of angina pectoris with a tissue vasodilator extract preliminary report	625
Wilcox, Reynold Webb	244		
Wile, Udo J		Wright, G A Pemberton	
Cutaneous manifestations of systemic diseases	1103	Standardization of American specialists	
Williams, John R		Editorial	805
The insulin co-efficient, an improved method for the clinical control of diabetes mellitus	264		
Willson, Hugh Spaulding	1332	YOUMANS, J B (with S S Riven)	
Winter, Henry Lyle	537	Hypothyroidism without myxedema	1497
Wolffe, Joseph B (with Donald Find-		Young, Joseph Witham	538

